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INTRODUCTION: Boron neutron capture therapy (BNCT) is a two-step binary therapy. First, the patient is injected with a tumor-localizing drug containing boron-10 (^{10}B), which has a high propensity to capture thermal neutrons. In the second step, the patient is irradiated with epithermal neutrons. After capture reaction, high-energy alpha particles and ^7Li particles are emitted with short pathlength (less than $10\mu\text{m}$). When a boron drug is concentrated in the tumor tissue, BNCT becomes cellular-based tumor selective radiation therapy [1].

Preclinical and clinical data show that radiotherapy sensitizes refractory tumors to immune checkpoint inhibitors, which has been proven to be effective in cancer treatment. In the past, radiotherapy was thought to be just local treatment. Now radiotherapy has an additional role: an enhancer of immunotherapy. Radiotherapy is now called “game changer” in this view point in immunotherapy [2].

So far no one knows how “immunologically active” BNCT is combining with immunotherapy and how host immune responses occur after BNCT in the tumor tissue and the surrounding normal tissues. Considering that BNCT is cellular-level particle therapy, the aim of this project is to identify novel immune reactions after BNCT compared to after conventional radiotherapy and other cancer therapies.

EXPERIMENTS:

Mice and cell lines: Luciferase-expressing B16F10 melanoma cells (B16-Luc), which were transduced with the luciferase gene in pLVSIIN-EF1apuro vector, was purchased from National Institutes of Biomedical Innovation, Health and Nutrition, JCRB cell Bank (Osaka, Japan). B16-Luc was maintained in DMEM (Nacalai Tesque, Inc., Kyoto, Japan) with 10% fetal bovine serum and penicillin/streptomycin (100 U/mL). SCC-VII, a squamous cell carcinoma cell line derived from C3H/He mice (Department of Radiology, Kyoto University), was maintained in Eagle's minimum essential medium (Nacalai Tesque, Inc., Kyoto, Japan) supplemented with 12.5% fetal bovine serum and penicillin/streptomycin (100 U/mL). The cells were cultured at 37°C with 5% CO_2 . All of the animal experiments were approved by the Animal Research Committee of Kyoto University and were performed in accordance with the institutional laboratory animal handling guidelines and the guidelines governing animal care in Japan. Mice were purchased from CLEA Japan (Tokyo, Japan). Syngeneic B16-F10 (2×10^5) or SCC-VII (2×10^5) were subcutaneously inoculated with Matrigel (Corning Inc., NY, USA) into the right hind legs of six-week-old C57Bl/6 or C3H/He mice, respectively.

Treatment: L-BPA and fructose were dissolved in distilled water at a molar ratio of 1:1.5, and then a 1.15 M ratio of 1 N NaOH was added. The mixture was stirred until L-BPA had completely dissolved, and the pH value was titrated to 7.6 with 1 N HCl. The solution was filtered through a $0.22\mu\text{m}$ syringe filter for sterilization (Merck Millipore, Massachusetts, USA). The final concentration was set to 30 mg/mL.

Tumor volumes were calculated using the formula $\pi/6 \times \text{Length} \times \text{Width} \times \text{Height}$. Treatments were started when the tumor reached a volume of $100\text{--}150\text{ mm}^3$ in the B16-Luc model and $150\text{--}220\text{ mm}^3$ in the SCC-VII model. For BNCT group, 500 mg/kg of BPA was subcutaneously injected into mice into the nuchal sites. Tumor was irradiated by thermal and epi-thermal neutron (5MW, Institutes for Integrated Radiation and Nuclear Science, Kyoto University) 45 min after BPA injection for 15 min. For in vivo depletion of CD8+ T cells, CD8+ cell-depleting antibody was injected intraperitoneally (i.p.) just before BNCT treatment, and was maintained by weekly injections thereafter. For BNCT + immunotherapy combination group, aPD1 antibody was administered i.p. just after BNCT treatment (Day 0) and once per week thereafter until Day 41 (7 weeks).

Statistical analysis: Statistical analyses were performed with GraphPad Prism software version 7 (GraphPad Software Inc.). A *P*-value of less than 0.05 was considered significant. One-way ANOVA and Tukey's multiple comparison test were used to compare multiple groups. Kaplan-Meier analysis was used when comparing survival data.

RESULTS:

Mean irradiated physical dose was 9.42 Gy (Thermal neutron: 0.482 Gy, epi-thermal: 0.051 Gy, fast neutron: 0.357 Gy, gamma-ray: 0.491 Gy, boron dose: $0.268\text{Gy}/^{10}\text{B}$ 1ppm, estimated boron concentration: 30 ppm).

In both B16-Luc and SCC-VII groups, CD8 depletion results in tumor regrowth 7 days after BNCT, while tumor continues to decrease in volume for at least 14 days in BNCT group. The combination of aPD1 antibody with BNCT shows significant better anti-tumor effect in both tumor models ($p < 0.05$).

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CO7-2 Boron nitride (^{10}B N) a prospective material for boron neutron capture therapy

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INTRODUCTION: Boron Neutron Capture Therapy (BNCT) is an expecting cancer therapy for the treatment of harsh and un-operatable malignant tumors. The efficiency of boron agent depends highly on tumor selectivity, sufficient amount of boron agent in tumor site, non-toxicity, tumour/normal tissues ratio (>3) and absorption of thermal neutrons by boron. Among a variety of bioceramics, boron nitride (BN) have remarkable properties that can be used as investigations for diagnostic purposes and drug delivery. In this study, ^{10}B was prepared using simple and cost effective solvothermal method to get the product with highest purity. BNCT studies were performed at Kyoto University Research Reactor Institute (KURRI).

EXPERIMENTS: Boric acid (^{10}B enriched with 99 atom% ^{10}B isotopic purity) and ammonia solution were used as boron source and nitrogen respectively to synthesize ^{10}B BN by solvothermal method. Details of experimental procedure and characterization are described in the literature.[1]

RESULTS: The structure is layered with B-N layers stacked over each other having very high surface area with electronegative atoms which makes this material highly dispersible in water. TEM images also shows that the particles are in 15–25 nm range interacting with each other.

MTT assay using HeLa, MCF-7, and HEK-293 cell lines was carried out. The results showed relatively less changes with lower concentration (150 and 300 $\mu\text{g}/\text{mL}$) of ^{10}B BN nanostructures, however up to 40 percent cytotoxicity rate was observed at higher concentration (1200 $\mu\text{g}/\text{mL}$). These results indicate that these nanostructures are not cytotoxic for tested cell lines at the concentration of up to 1 mg/mL and can be used for biomedical application at safe concentration below the studied doses.

Intracellular boron concentration was detected and results confirm the presence of boron inside cells. Boron content of cells treated with 25 ppm and 100 ppm concentration was 0.57 ppm and 1.9 ppm respectively. These results indicate concentration dependent uptake of boron in HeLa cells and ability to enter in intracellular environment.

BNCT study of ^{10}B BN was studied in comparison to L-BPA. Fig. 1(a) shows the schematic representation of 96-well plate irradiation. HeLa cells treated with ^{10}B BN shows almost similar dose-dependent cell killing effects as L-BPA at neutron fluence range of $3.6\text{--}6.3 \times 10^{12}/\text{cm}^2$ (Fig.1(b)). Thermal neutron fluence of $\sim 6.3 \times 10^{12}/\text{cm}^2$ resulted in almost 50% cell death of ^{10}B BN treated cells.

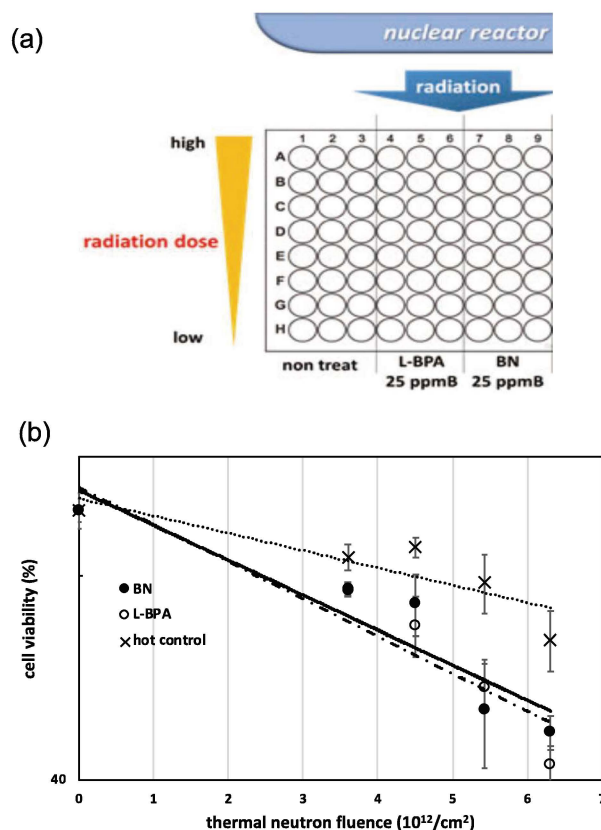


Fig. 1. (a) Schematic representation of irradiation to 96 well plate. (b) BNCT effect of ^{10}B enriched BN on HeLa cell lines in comparison to L-BPA.

CONCLUSION: The aim of present work was to synthesize ^{10}B enriched nanostructured boron nitride from boric acid and ammonia solution. BN was synthesized by solvothermal method at $650\text{ }^\circ\text{C}$ for 24 hours. The decomposition of ammonia solution produces hydrogen which is responsible for BN formation even at relatively low temperature. BNCT studies of boron nitride were performed using thermal neutron source on HeLa cells in comparison to L-BPA. The thermal neutron fluence of $\sim 6.3 \times 10^{12}/\text{cm}^2$ resulted in almost 50% cell killing of BN treated HeLa cells. These results show that ^{10}B enriched BN can be used as a potential candidate for BNCT.

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CO7-3 A Fundamental Investigation on Contents of Important Elements for Activation in Various Concrete

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INTRODUCTION: One of the typical materials for radiation shield is concrete at the points of its flexibility, sufficient supply, and inexpensiveness. On the other hands, once radiation facilities with shielding concrete start to operation, the concrete are affected by the radiation ray from the operating radiation source in the facilities and activated. Various types of low activation concrete[1]-[3], which are typically white cement based concrete, are the one of the ways to solve the problem. Especially, boron neutron capture therapy (BNCT) should be effective facilities to apply the low activation concrete.

METHODS: Various types of concrete samples were crushed to certain size (typically under 0.7mm or less), and were packed for 0.1 to 0.3 g with special treatment for the irradiation in KUR. After the irradiation with 10 to 60 minutes and with the certain cooling period, these samples were measured by Ge detector one by one. The quantity of the target elements, which were selected by former investigations as Co, Cs, Sc, Fe and Eu[1]-[3], in each sample were estimated by the comparison of the known standard material in the same package for the irradiation.

RESULTS: Figure 1 shows the correlation of the sample preparation procedures (typical and additional with disc mill) for measured contents of elements and introduces each result by two preparation methods is similar. Metal disc mill was used for crushing the samples additional to typical procedure samples, in order to reduce the grain size down to a few tenth micrometer. Figures 2 and 3 show the distribution of Eu, Co, and Cs contents in white cement based concrete (39 samples) and ordinary concrete (52 samples).

CONCLUSION: More than 200 concrete samples were prepared for estimating the contents of Eu, Co, and Cs, including investigation of preparation of the samples. These data would contribute the establishment of material data for shielding materials.

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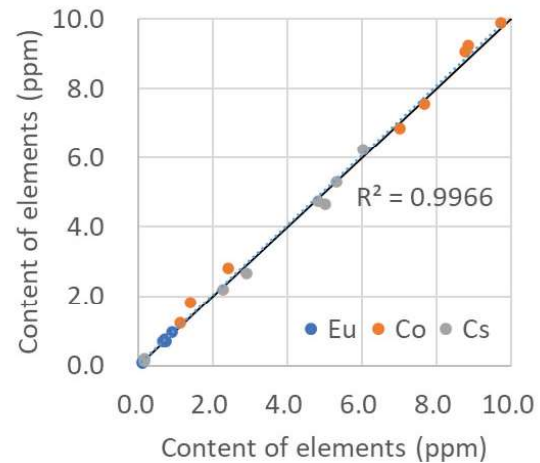


Fig. 1. Correlation of different preparations of sample.

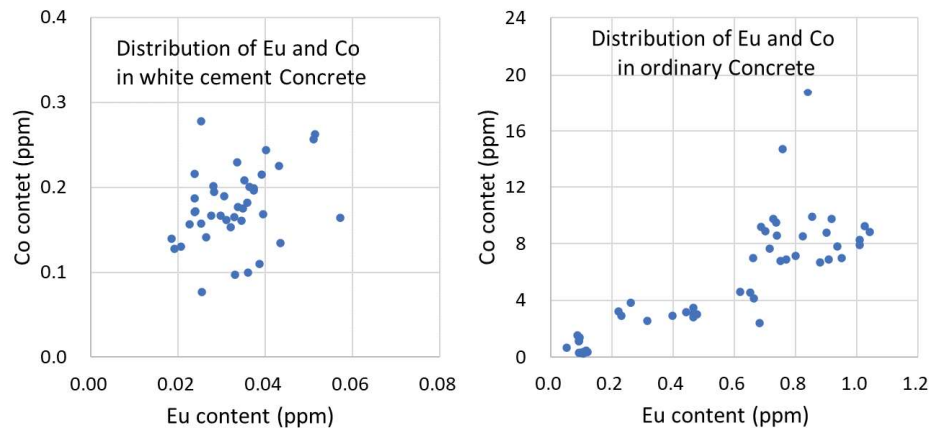


Fig. 2. Distribution of Eu and Co in various concrete.

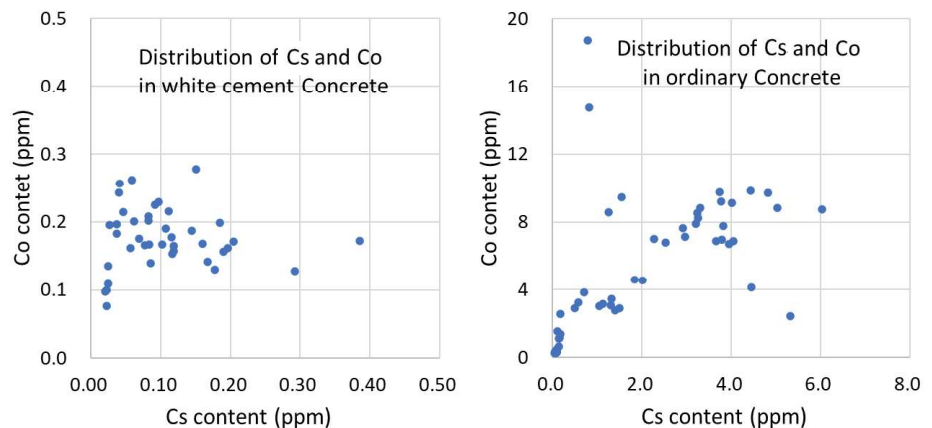


Fig. 3. Distribution of Cs and Co in various concrete.

Evaluation of the abscopal effect observed by mouse head irradiation following thermal neutron irradiation

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INTRODUCTION: The effect of metastasis of lymph nodes such as lymph nodes in areas that are not irradiated sites in radiation therapy of malignant lymphoma is reported in 1953 and is called abscopal effect. Abscopal is a Latin meaning of "far away" ab and the ancient Greek "target" scopal, a phenomenon that collectively refers to the indirect effects of radiation on sites that are not the sites of the irradiation. It is reported about the abscopal effect in radiotherapy that immune response is activated by partial radiation [1]. The influence on immune organization of the mouse at the time of the head irradiation is not well known. The purpose of this study is to evaluate the relative biological effectiveness in the severe combined immunodeficiency (SCID), so-called SCID mice, those are having well-known high radiation sensitivity comparing with C3H/He mice having normal radiation sensitivity.

EXPERIMENTS: CB17/Icr-Prkdc^{scid}/CrICrIj (SCID mice) were obtained from Charles River Inc. As a comparison experiment for the SCID mice, C3H/He mice were obtained from Japan Animal Inc.

Neutron irradiation was performed as follows. The Heavy Water Facility of the Kyoto University Research Reactor (KUR) was used. Mice were restrained in a plastic box on a radiation board. Neutron fluence was measured by radio-activation of gold foil and gamma-ray doses by TLD. Mice were restrained in a plastic box on an acrylic plate. In order to irradiate the head of the mouse, the mice head was left radially to the irradiation area of the plate. Gold and TLD placed on the head and abdomen, respectively. The mice were fixed on tape and the acrylic plate and mice were covered with a plastic bag to prevent the escape. After irradiation, the splenic cell suspension was adjusted and incubated. At 48 hour, 72 hours after irradiation, apoptotic induction of the cells was examined by Cell Death Detection ELISA (Roche).

RESULTS: As shown in Table 1, the apoptotic change with radiation dose. The apoptotic induction of the splenocytes of SCID mice was larger than that of C3H mice at 48 hours and 72 hours after irradiation. The difference of the apoptosis of the splenic cells between SCID mice and C3H mice was larger at the 72 hours than 48 hours after the neutron radiation.

Table1. Apoptotic induction of the splenocytes at 48 and 72 hours after neutron irradiation*

Radiation dose	SCID		C3H	
	48 h. after radiation	72 h. after radiation	48 h. after radiation	72 h. after radiation
control	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1
0.5Gy	1.5 ± 0.1	1.8 ± 0.2	1.1 ± 0.1	1.1 ± 0.1
1.0Gy	2.1 ± 0.2	2.5 ± 0.2	1.5 ± 0.1	1.1 ± 0.1

*Each data shows the enrichment factor at neutron radiation dose. Each data shows the mean value ± SD.

DISCUSSION

Previously we reported the RBE values for SCID mice of the LD50 by radiation oral death assay and gamma H2AX foci number of the lymphocytes. The RBE values calculated from radiation oral death assay and gamma H2AX foci number of the lymphocytes were 1.6 for SCID mice and 2.0 for C3H mice [2]. The SCID mice show extreme sensitivity to ionizing radiation, because cells lack functional DNA-dependent protein kinase. In this study, our results suggest that the abscopal effect for SCID mice were larger than C3H mice. The difference of the apoptosis of the splenic cells between SCID mice and C3H mice was larger on the time dependent. That is to say, the hyper radiation sensitivity was observed in the abscopal effect after the neutron irradiation.

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CO7-5 The feasibility study of Eu:LiCAF neutron detector for an accelerator-based BNCT

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INTRODUCTION: The stability of neutron flux at an accelerator-based BNCT facility is relatively worse than that at a reactor-based one. Therefore, it is necessary to measure the neutron flux precisely in real-time to optimize the patient's exposure dose for the accelerator-based BNCT. However, the neutron flux is so intense (about 10^9 (n/cm²/s)) that the real-time measurement has not been realized yet. Hence we tried to measure the neutron flux with a small detector using a Eu:LiCAF scintillator [1] on the tip of optical fibers, as shown Fig.1. We reported that this detector has the linearity to the neutron flux to 10^9 (n/cm²/s) in our previous article [2]. In this

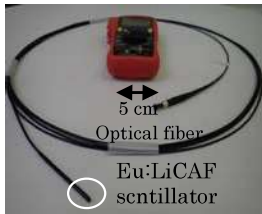


Fig. 1 Detector coupled with the optical fiber.

experiment, we tried to check the linearity for neutron flux up to 10^{11} (n/cm²/s) using the KUR-SLY, and to check it can be used not only exposure dose monitor but also beam monitor.

EXPERIMENTS: The experiments were performed at the KUR-SLY where the maximum neutron flux of about 10^{12} (n/cm²/s) is available at the bottom when the reactor power is 1MW [3]. Figure 2 shows the experimental set-up for the measurement, where the photon counting unit C8855 and 994 is able to count up to 1 Mcps. The optical output from the Eu:LiCAF scintillator through the optical fibers was properly converted to an electric signal and counted with the counting units. Prior to the measurement, the detector was put into the plastic bottle, where Figure 3 shows the situation, and loaded to 47 cm from the bottom of the KUR-SLY. At this position, the maximum neutron flux is about 1.8×10^{10} (n/cm²/s). First experiment was carried out from the starting-up to 1 MW-arrival of the reactor. Next, after arrived at 1MW, we changed the detector position in the KUR-SLY, to measure counting of different neutron fluxes using the

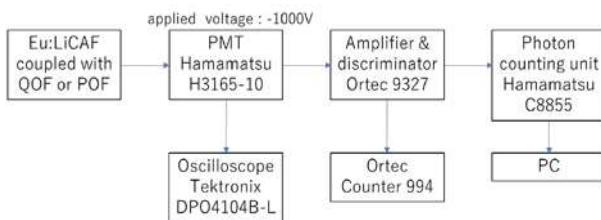


Fig. 2 Experimental setup.

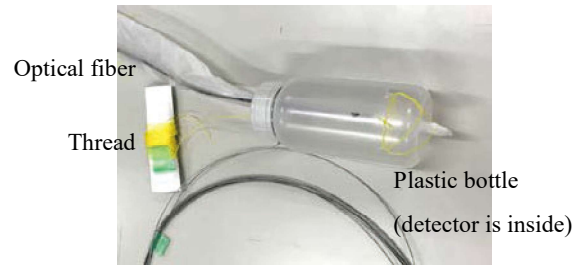


Fig. 3 Situation about the putting into the plastic bottle.

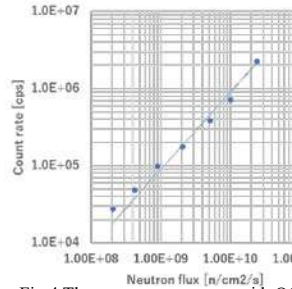


Fig.4 The neutron count rate with QOF

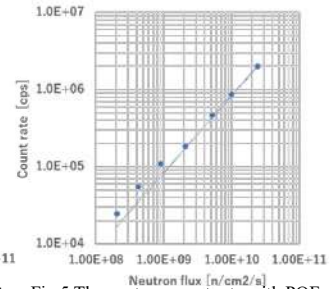


Fig.5 The neutron count rate with POF

detector coupled with the quartz optical fiber (QOF) or the plastic optical fiber (POF).

RESULTS: The count rate using the detector coupled with QOF was varied according to reactor power during the reactor power rises to 1MW from starting-up. Figure 4, 5 show the neutron count rate using QOF and POF respectively with the detector. The results indicate the detector coupled with QOF or POF have approximately linearity to the neutron flux up to 2×10^{10} (n/cm²/s).

CONCLUSIONS: We developed detector which is small detector using a Eu:LiCAF scintillator on the tip of optical fibers, and confirmed that the detector coupled with QOF has the same performance as the detector coupled with POF. The detector can measure neutron flux of 10^8 to 2×10^{10} (n/cm²/s), therefore it can be used not only exposure dose monitor but also beam monitor for accelerator-based BNCT facility.

It is confirmed that QOF is more radiation-resistant than POF [4]. We are planning to conduct experiments to confirm the detector coupled with QOF have enough radiation-resistance for practical use in the future.

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CO7-6 Enhancement of the cancer cell-killing effects of boron neutron capture therapy by overexpression of *LAT1* in human cancer cells

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INTRODUCTION: Outcome from BNCT largely depends on amount of intracellular accumulation of boron compound. L-type amino-acid transporter 1 (LAT1) [1], through which boronophenylalanine (BPA) is transported into cells, is frequently expressed in various types of tumor cells including glioblastoma but not in normal cells [2]. We transfected *pCMV/LATI-GFP* plasmids into a glioblastoma cell line, T98G, and selected several clones and confirmed that those clones stably overexpress LAT1 in cell membrane with confocal laser microscopic observation and western blot analysis. In this study, we measured the sensitivity to the neutron and gamma-ray fluences generated by KUR in T98G/K1 and T98G/K4 clones that uptake ¹⁴C-BPA 2.5 and 5.0 times, respectively, larger than T98G/KC2 control clone.

EXPERIMENTS: T98G/K1, T98G/K4, T98G/KC2 and transiently *pCMV/LATI-GFP*-lipofected T98G/KC2 cells (treated with Lipofectamine 2000 overnight) were treated with medium containing ¹⁰BPA (0, 5 or 20 ppm) for 3 hours. The cells were trypsinized and the cell suspensions in 1.5-ml cryo-tubes were irradiated with the fluences (0.4 or 0.8 Gy in total doses of neutrons and γ -rays) from KUR. The irradiated cells were plated on three replicate dishes for colony formation assay. The cells were fixed

with ethanol and stained with crystal violet after cell culture for 10-14 days.

RESULTS: T98G/K4 cells showed slightly enhanced sensitivity to the fluences compared with T98G/K1, T98G/KC2 and the lipofected T98G/KC2 cells in the case of 5 ppm ¹⁰BSA treatment. There is no significant difference in the sensitivity between T98G/K1 and T98G/KC2 cells as well as transiently lipofected T98G/KC2 cells. In the case of 20 ppm ¹⁰BSA treatment, T98G/K4 and the lipofected T98G/KC2 cells showed largely enhanced sensitivity to the fluences compared with T98G/KC2 cells (ER=1.5). T98G/K1 cells showed slightly enhanced sensitivity (ER=1.2). The sensitivity of the cells to the fluences was correlated with the expression level of LAT1 of the cells. Figures of results are now in preparation for publication in journal.

CONCLUSION: This study showed that overexpression of LAT1 in cancer cells causes enhanced anticancer effects of BNCT and BNCT combined with gene therapy is beneficial for tumors bearing low LAT1 expression.

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CO7-7 Clinical Outcome of BNCT for Advanced or Recurrent Head and Neck Cancer

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Introduction: We report outcome of BNCT for AHNC (advanced head and neck cancer) and RHNC (recurrent head and neck cancer). The principal endpoints specified in this study were progression-free and overall survival consequences.

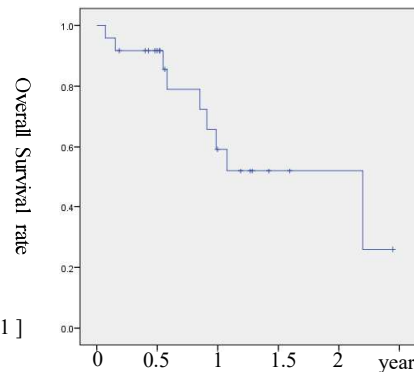
Methods: 24 patients (25 cases) were included in this study and received BNCT between Aug. 2017 and Feb. 2019. One patient was received BNCT twice, because of tumor progression after first BNCT. Characteristics of the patients are detailed in Table1. FBPA-PET was under-gone in all cases to determine the indication for BNCT, and the median T/B ratio was 3.2 (range 2.5-8). 13 patients had received systemic therapy (ST), such as nivolumab, cetuximab or TS-1, and the therapy had been continued for 6 months after BNCT. Overall survival (OS) time was measured from the date of BNCT until confirmed death or the date of the last follow-up examination.

Results: Median follow-up of surviving cases was 8.7 months (range 0.9-29.8). At the time of analysis, 15 patients (62.5 %) were alive, and 9 patients (37.5%) out of them were alive with no evidence of disease. The local recurrence was occurred in 12 patients, and a median time to recurrence was 4.8 months (range 2.7-15.4). Nine patients died during an observation period, and eight of them died of disease progression. 1year OS and progression free survival (PFS) rate was 50.0% (Fig 2.) and 59.2% (Fig 1.), retrospectively. 1year OS rate of ST group and non-ST group was 77.8% (median time 12.5 months) and 32.7% (median time 6.3 months) respectively ($p=0.039$) (Fig.3). 1year PFS rate of ST group and non-ST group was 65.9 % (median time 11.6 months) and 25.0 % (median time 3.6 months) respectively ($p=0.075$) (Fig.4). There were no associations between the number of T/B ratio and OS rate, either PFS rate. An addition of ST to BNCT did not increase any adverse effects.

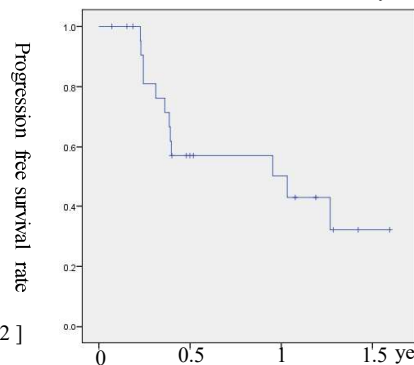
Conclusion: BNCT is effective in the treatment of locally recurred head and neck cancer.

[Table 1]

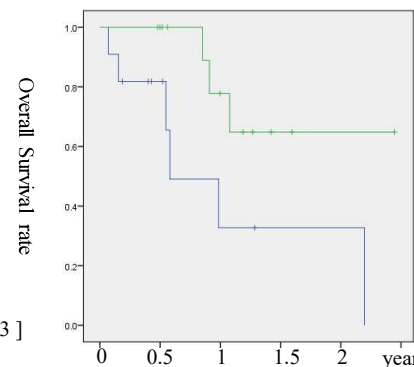
		Number of patients
Sex	Male / Female	10 / 14
Age	Median(range)	53 (34-78) years
Histology	SCC/ Non-SCC	18 / 6



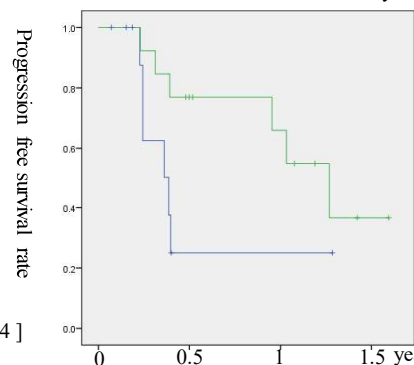
[Fig. 1]



[Fig. 2]



[Fig. 3]



[Fig. 4]

CO7-8 Establishment of a novel mutation breeding using Boron Neutron Capture Reaction (BNCR)

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INTRODUCTION: Boron Neutron Capture Reaction (BNCR) is based on the nuclear reaction of ¹⁰B atom with thermal/epithermal neutron already applied to cancer treatment (BNCT) [1, 2]. As a new utilization method of BNCR, the purpose of this study is to establish a novel mutation breeding using BNCR.

This method uses the principle of inducing mutation by an alpha particle and ⁷Li recoil nuclei high linear energy transfer and short range when irradiated with neutrons (low energy thermal neutrons (< 0.5 eV) can be absorbed the ¹⁰B atoms, leading to generating high linear energy transfer alpha particles (~ 150 keV/μm) and ⁷Li nuclei (~ 175 keV/μm) that are produced by BNCR of ¹⁰B selectively taken into the meristematic cell with thermal neutron. This principle is different from both chemical mutagens, such as EMS and MNU, and physical mutagens, such as gamma rays and ion beams, used for mutation breeding so far. In other words, the mutagenic effect depends on chemical and physical factors, such as ¹⁰B concentration, thermal neutron intensity, and irradiation time.

The germination rate is used as one of the traits to verify the effect of mutagenesis[3]. The immersed into BPA but not irradiated with neutrons seeds were germinated normally at different concentrations (0, 10, 100, 200ppm) of BPA in the range of from 70% to 100%. This time, it was confirmed that the germination rate was affected a thermal neutron fluence-dependent or a BPA concentration-dependent manner by causing BNCR.

EXPERIMENTS: The experimental material used *Oryza sativa* L. cv. Nipponbare. The dry seeds were immersed into different concentrations (0, 10, 100, 200ppm) of ¹⁰B-enriched *p*-boronophenylalanine (BPA)[4] for 16 h. Some concentrations were also tried with hulled rice. The samples were washed with water and re-dried at room temperature. The seeds in 2-mL tubes were irradiated with thermal neutron for 90 minutes in the Kyoto University Research Reactor (KUR). To provide four different levels of neutron fluence, the tubes were set to four columns microtube rack at the time of irradiation. After the irradiation treatment, the seeds were cultured in pe-tri-dishes with continual moistening of filter paper at 25°C under a photoperiod of 16 h light and 8h dark, it was investigated the germination rate.

RESULTS: The typical thermal neutron fluence were 1.1x10¹³ cm², 8.1x10¹² cm², 6.0x10¹² cm², 4.2x10¹² cm², at the time of irradiation. The germination rate not de-

creased with both thermal neutron fluence and BPA concentrations (Table 1, 2). That is, the meristematic cell in the seeds were not damaged enough to initiate cell division in the range of the present experimental conditions. Besides, using hulled rice, the samples were fragile due to re-drying. The hulled rice was not suitable for this method. We are set to confirm conditions for making a strong effect by making the fructose complex higher BPA concentrations and extending the immersion time. By investigating inhibition of germination and reduction in survival of the samples, we will consider the suitable conditions as a mutagenesis method.

Table 1. The relationship between thermal neutron fluence and germination rate.

Thermal neutron fluence	Concentrations of BPA (ppm)	No. of seeds	No. of seeds germinated	germination rate (%)
high ▼ low	0	37	31	84
		35	32	91
		38	28	74
		40	29	73
high ▼ low	10	38	30	79
		35	27	77
		37	27	73
		33	26	79
high ▼ low	100	35	26	74
		40	31	78
		36	29	81
		36	31	86
high ▼ low	200	35	26	74
		35	27	77
		35	26	74
		36	30	83

Table 2. The relationship between BPA concentrations and germination rate.

Concentrations of BPA (ppm)	No. of seeds	No. of seeds germinated	germination rate (%)	germination index
0	150	120	80	100
10	143	110	77	96
100	147	117	80	99
200	141	109	77	97

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- [3] Tanaka A. *et al.*, Int. J. Radiat. Biol., **72**, (1997), 121-127.
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INTRODUCTION: BNCT have been applied to recurrent malignant glioma and even after standard therapy (surgery, chemo-radiation therapy) because of the selective damage to the tumor. Especially, glioblastoma (GBM) is the most miserable cancer, whose patient survival is 14.6 months and remarkably resistant to chemo-radiation and immuno-therapy. With BNCT, we achieved better local control and survival benefit in malignant glioma using thermal neutrons produced by the reactor in Kyoto University. However, the recurrence is inevitable after BNCT. Reasons for recurrence after BNCT have not been fully elucidated, but they may reflect tumor characteristics. In fact, we've found cerebrospinal fluid dissemination, frequent cause of death, after BNCT occurs more frequently in the small cell subtype of IDH1R132H mutation-negative glioblastoma [1]. On the other hand, exosomes, extracellular vesicles with diameter of between 50 nm to 150 nm used for communication tools between cells, are receiving a lot of attention because containing microRNAs, lipids and proteins are possible biomarker for various diseases. In this study, we investigate the exosomes from glioma cells after BNCT.

EXPERIMENTS:

Cell culture: U87 MG glioma cells were cultured with exosome-free fetal bovine serum (FBS) at 10 % final concentration in Dulbecco's Modified Eagle's Medium (DMEM) at 37 °C in 5 % CO₂ incubator for two days. Cells were divided into four groups, control, Boronophenylalanine (BPA) alone, thermal neutron irradiation alone, and BNCT. BPA was added to the medium at 25 ppm the day before irradiation. One group consisted of more than 3×10⁶ cells.

Thermal neutron irradiation: After trypsin treatment, cell suspensions were divided in Eppendorf tubes at 1×10⁶ cells/mL with exosome-free FBS at 10 % final concentration in DMEM with or without 25 ppm BPA and irradiated with thermal neutrons at D₂O facility for one hour.

After irradiation, cells were centrifuged to change the medium, then dissociated into 10cm dishes with exosome-free FBS at 10 % final concentration in DMEM (1×10⁶ cells / dish).

Exosome isolation: 48 hours after irradiation, cell culture medium (CCM) of each group was collected and centrifuged to remove the cell debris at 2000 rpm for 20 min at 4 °C. The supernatant was removed without disturbing the pellet and filtered through 0.22 μm filters (Merck Millipore) to remove contaminating remaining microvesicles, and cell debris and kept in – 80 °C deep freezer.

After thawing, the CCM was concentrated to 500 μL with Centrifugal Filter (Amicon Ultra-15, 100 kDa) devices at 4 °C. Following this, 500 μL of CCM was overlaid on qEV size exclusion columns (IZon) and exosome containing fractions were collected. Exosome fractions were pooled and concentrated in Amcon Ultra-0.5 10 kDa molecular weight centrifugal filter units to a final volume of 50 μL. Purified exosomes were then store at – 80 °C until use.

Tunable resistive pulse sensing: The size distribution profile and concentration of exosomes were analysed with tunable resistive pulse sensing (TRPS) (qNano, IZon Science Ltd). Carboxylated polystyrene beads (70 nm) were used to calibrate the concentration and size.

RESULTS:

The exosomes size distribution and concentration of each group was assessed by TRPS. Exosome size from all groups have the typical range of between 50 to 150 nm in diameter (Fig.1). Concentrations of exosomes of each group: control, BPA alone, thermal neutron irradiation alone, and BNCT, were 2.68 ×10⁹, 1.89×10⁸, 1.84×10⁹, 1.18×10⁸(/mL), respectively.

The contents of exosomes are to be analyzed by proteomics.

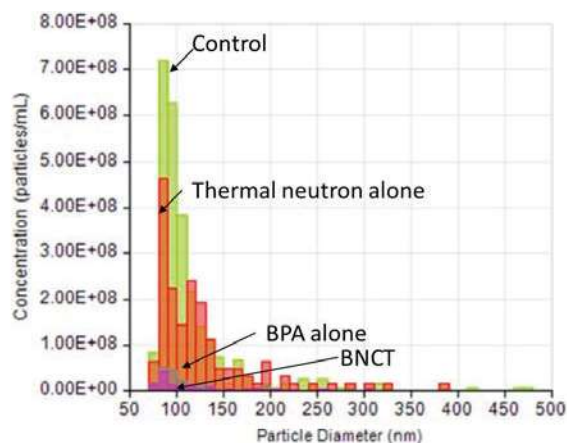


Fig. 1: TRPS analysis of exosomes confirming the size range of 50-150 nm in diameter. (Arrows indicate each group.)

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[1] Kondo N, *et al*, 2017, J Neurooncol. 2017;133: 107-118. doi: 10.1007/s11060-017-2408-x

CO7-10 iPS cells - derived neuronal cell death and inflammation by thermal neutron irradiation

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INTRODUCTION: Biological effect of thermal neutron irradiation on neuron is unknown. Thermal neutron is used for clinical treatment for Boron Neutron Capture Therapy (BNCT). To avoid radiation brain necrosis after BNCT, we investigate the pathway of cell death and inflammation induced by BNCT using human induced pluripotent stem cells (iPSCs)-derived neuronal cells.

EXPERIMENTS:

Cell culture: We used human iPSC-derived Neural stem/progenitor cell (NSPC) lines [1]. We differentiated these iPSC derived NSPCs and seeded into laminin-coated 8 well chambers and T25 flasks. Cells were sealed and transferred from the Osaka national hospital to KURNS the day before irradiation kept at 24 °C in the box and cultured at 37 °C CO₂ incubator after transfer.

Thermal Neutron Irradiation: We irradiated thermal neutron irradiation to these cells with sealing for 30 minutes at room temperature by D₂O facility.

Cell death assay: We stained the cells in 8 well chamber 24 hour after irradiation with Hoechst 33342, Annexin V-FITC and Propidium Iodide Solution following the manufacture's protocol (nacalai tesque, Japan) and captured them by the microscope [Keyence BZ9000].

Sampling for RNA isolation: We rinsed the cells in T25 flasks with PBS 24 hours after irradiation and lysed them with QIAzol following the manufacture's protocol (QIAGEN, Japan) and kept the cells at – 80 °C deep freezer.

RESULTS: We are still analyzing the results.

REFERENCES:

[1] Fukusumi *et al.* (2018), Peer J, DOI 10.7717/peerj.4187

CO7-11 Resistant Mechanism of Glioma Conferred by Tumor Microenvironment after BNCT

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INTRODUCTION: BNCT have been applied to recurrent malignant glioma and even after standard therapy (surgery, chemo-radiation therapy) because of the selective damage to the tumor. Especially, glioblastoma (GBM) is the most miserable cancer, whose patient survival is 14.6 months and remarkably resistant to chemo-radiation and immuno-therapy. With BNCT, we achieved better local control and survival benefit in malignant glioma using thermal neutrons produced by the reactor in Kyoto University. However, the recurrence is inevitable after BNCT. Reasons for recurrence after BNCT have not been fully elucidated. In this study, we investigate the crosstalk between tumor microenvironment cells and tumors which survive after BNCT.

EXPERIMENTS:

Cell culture: We used mouse G261 glioma cell line and human glioma GBM1 line. Cells were cultured at 37 °C in CO₂ incubator.

Xenograft model

Animals were anesthetized and immobilized in a small animal stereotactic device. 2×10^5 cells were transplanted through a hole 2 mm to the right of the bregma, at a depth of 3 mm, at a rate of 1 micro L/min. G261 were transplanted to C57BL/6J mice and G261 were transplanted to Balb/cA-nude mice.

Boronophenylalanine (BPA) Treatment and Thermal

Neutron Irradiation: After 10 days from transplantation, 500mg/kg of BPA was administrated subcutaneously 1 hour before irradiation. We irradiated thermal neutron to these mice shielding body trunk with lithium fluoride for 15 minutes at room temperature by D₂O facility with 5MW power.

Sampling for Immunohistochemistry: 48hours and 7 days after irradiation, mice were anesthetized and sacrificed after transcardiac perfusion of PBS and 4 % paraformaldehyde (PFA). The brain tissue was removed and fixed with 4% paraformaldehyde overnight, then transferred to 30 % sucrose in PBS. The tissue blocks were frozen at -80 °C.

RESULTS: We are still analyzing the results.

CO7-12 Improvement of the method for analysis of micro boron distribution in tissues

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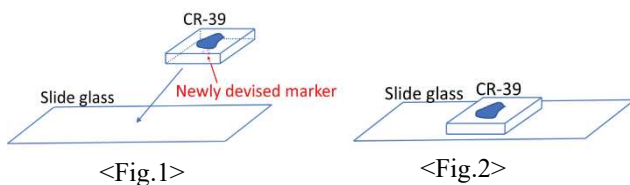
INTRODUCTION: In the process of ARG, we need to acquire tissue staining image and etched pit image separately and merge them using its markers. So precise marking system is the essential for precise analysis. But in the etching process, ordinary markers using ink are easily disappeared. To avoid disappearing the markers, we used scratch markers on the CR-39 since scratch remains after etching process [1].

However, in chemical etching process, scratch marker is also etched, and the marker become larger. Because the shape of the marker is deferent before and after etching, the preciseness of matching image is not good enough.

In this study, we devised new marking system, of which the marker deformation before and after etching is minimal by keeping the marker away from the etching solution. Here, we report the method of the newly devised marking system and the assessment the precision of it.

EXPERIMENTS: The process of ARG using newly devised marking system is shown as bellows.

1. Put the tissue section on the CR-39 and irradiate them with thermal neutron.
2. Put small marker using ball-point pen near the place to be analyzed, on the opposite side of tissue section. <Fig.1>
3. Put the CR-39 on the slide glass using epoxy adhesives, which has good chemical resistance. In this process, the marker should be inside between CR-39 and slide glass. <Fig.2>
4. Stain the tissue section and acquire both tissue image and corresponding marker image using optical microscope.
5. Remove the tissue section from the CR-39.
6. Etch the CR-39 chemically and acquire both the etched pit image and corresponding marker image.
7. Merge two images (acquired in process 4 and 6) using its markers.



In the experiment, we used CR-39 (BARYOTRAK) and acquired their images using microscope (Keyence BZ-9000). Automatic marker matching program was created and tested.

Marker deformation before and after chemical etching

- We defined maximum deformation length (dL) between before and after etching marker as bellows.



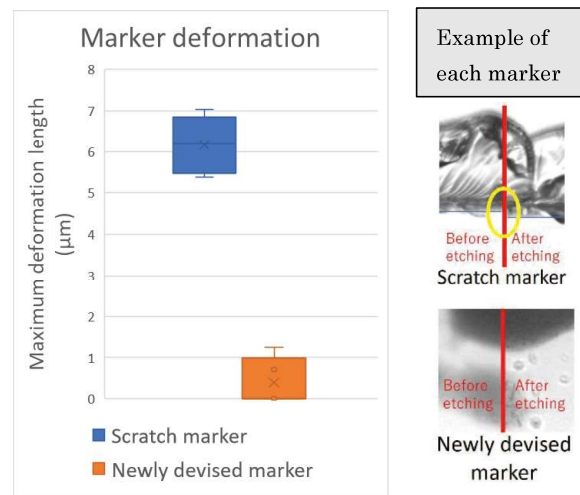
$$dL = \sqrt{dx^2 + dy^2}$$

dx: size difference of horizontal direction

dy: size difference of vertical direction

- The maximum deformation length means maximum potential error in matching images using the markers.
- Five samples are assessed.

RESULTS: The maximum deformation length of each marking method is shown as bellows. The average maximum deformation length is 6.17 μ m and 0.39 μ m for scratch marker and newly devised marker, respectively.



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1. H.Tanaka *et al. J. Radiat. Res.* **55**, (2014) 373–380

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INTRODUCTION: Whole organ irradiation in radiotherapy is effective on multiple tumors and minimal residual tumors, such as whole brain irradiation for brain metastasis, whole conserved-breast irradiation in conservative therapy for breast tumor, etc.. However, it cannot be realized for liver and lung tumors. It is because the tolerant dose of these organs is 20 to 40 Gy, which is smaller than the tumor control dose of 50 to 80 Gy. In BNCT, the ranges of the heavy charged particles due to the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction in the boron compound, which selectively accumulates in tumor cells, are too short to reach the adjacent normal cells. Therefore, BNCTs with the whole organ irradiation for liver and lung tumors can be realized as radiotherapy.

In BNCT clinical studies for liver and lung tumors at KUR, the equivalent doses for normal liver and/or lung have been estimated on the basis of boron concentration in blood, which is measurable by prompt gamma-ray analysis. But actually, the variation for the boron concentration in normal liver and/or lung is assumed to be larger among the patients with basal disease, such as cirrhosis, pulmonary fibrosis, pulmonary emphysema, etc..

The purpose of this research is the development of the real-time boron-concentration estimation system in liver and/or lung during BNCT, in order to improve the dose estimation accuracy for BNCTs with the whole-liver and/or whole-lung irradiation. In this system, the technique of prompt gamma-ray telescope is applied. A gamma-ray telescope system has been in use for liver tumor BNCT at Heavy Water Neutron Irradiation Facility of KUR (KUR-HWNIF) from 2005 [1]. The collimation system of this telescope was improved in 2017.

An experiment was performed to confirm the basic characteristics of this improved telescope system in 2019.

METHODS: Figure 1 shows the outline of the original gamma-ray telescope system. A 100 cm-long collimator is located in the hall through the irradiation-room ceiling wall. The first collimator is settled just before the detector, and the second collimator is settled at the bottom of the collimation system. In the improved system, both collimators are placed in the collimation system. The distance between these collimators is changeable.

The layout of the characterization experiment was almost similar to the layout in Fig. 1. Instead of a patient, a whole-body liquid phantom was placed. This phantom was the 1-cm-thick acrylic case filled with boric acid water. The boron concentration of the boric acid water was 25 ppm for boron-10. A higher-concentration spheri-

cal region of 5 cm in diameter was settled in the phantom. This region was modelled after a tumor part, and its boron concentration was 250 ppm. The standard epi-thermal neutron irradiation mode was used for this experiment. For the positions of the first and second collimators, the prompt gamma-rays due to $^{10}\text{B}(n,\alpha)^7\text{Li}$ and $^1\text{H}(n,\gamma)^2\text{D}$ reactions were counted by the high-purity germanium (HPGe) detector settled on the irradiation room ceiling.

RESULTS: Figure 2 shows the ratio of the prompt gamma-ray counts of boron-10 to hydrogen-1 for the collimator interval. In this case, the collimator position is settled to be highest, and the second collimator moves from the highest position to the lowest position. As the second collimator position is lower, the collimator interval is larger and the telescope FOV is smaller. As shown in Fig.2, the count ratio is smaller as the collimator interval is larger. This reason is considered to be the influence of the position of the higher-concentration region in the telescope FOV. It is thought that the higher-concentration region gradually goes out from the telescope FOV, according to the increase of the collimator interval.

CONCLUSION: The basic characteristics of the improved telescope system were experimentally confirmed. The further analyzation of the experimental data and the additional experiments are planned.

ACKNOWLEDGEMENTS: This study was supported by The Kyoto University Research Fund (Core Stage Back-up, in 2017).

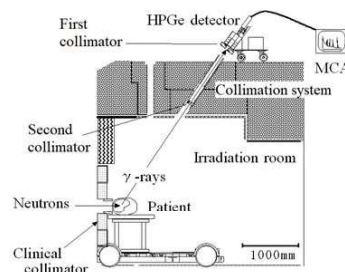


Fig. 1. Outline of the original gamma-ray telescope system installed at KUR-HWNIF.

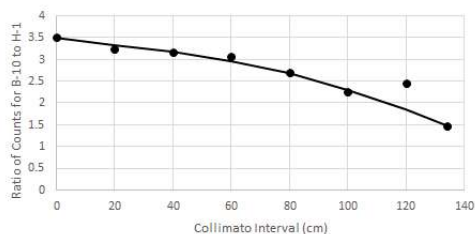


Fig. 2. Ratio of gamma-ray counts for B-10 to H-1.

REFERENCES:

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CO7-14 Establishment of protocol for neutron capture therapy for head and neck cancer

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INTRODUCTION: Neutron capture therapy (BNCT) for head and neck tumors has been clinically studied since 2001, with the BNCT research group at Kyoto University Reactor Laboratory, which is a co-investigator, highly effective, with high safety. It is being established. Since November 2012, we implemented the therapy as a joint research with Kyoto University Reactor Laboratory, with the consent of the patients in 4 cases of refractory recurrent head and neck cancer. As a result, the response rate was a very high 100%. The tumor reduction effect in recurrent cases after radical irradiation, which could not be achieved by conventional treatment methods, strongly suggests the possibility of expanding the indications for BNCT for refractory carcinomas as well as for head and neck cancer cases. Here, we will perform BNCT for refractory and recurrent head and neck tumors and examine their efficacy and optimal protocol.

EXPERIMENTS: We will treat BNCT for refractory and recurrent head and neck tumors that meet the following criteria and examine their efficacy and optimal protocol.

Inclusion Criteria

- (1) The patient with local recurrence of head and neck cancer who can not perform the standard therapy any more after radiotherapy.
- (2) The patient with local recurrence of head and neck cancer by the imaging diagnosis, such as CT, MRI and PET.
- (3) The patient with previous radiotherapy (total 40-75 Gy, 2Gy/fq) for the recurrent region.
- (4) The patient with the period of more than one month since the previous treatment.
- (5) The patient with recurrence lesion in the less than 6cm of depth from skin as GTV for BNCT.
- (6) The Patients who have PS less than 2 and are expected to survive more than 6 months after BNCT.
- (7) The patient with good condition of renal function: creatinine <1.2 mg/dl for male and <1.0 mg/dl for female.
- (8) The patient with the age between 20 and 80.
- (9) Written informed consent with one own will.

Exclusion Criteria

- (1) The patient with active multiple primary cancers; synchronous or metachronous (within 5 years) double cancers .
- (2) The patient with metastatic lesion.
- (3) The patients with severe complications.
- (4)The patients with infection requiring systemic treatment.
- (5) The patient with severe adverse event (>Grade3, CTCAE v4.0) in the BNCT region.
- (6) The patient with cardiac pacemaker.
- (7) The patient judged to have difficulty in maintain posture during the protocol treatment.
- (8) The patient with WBC; < 3000/mm³, PLT; < 100000/mm³
- (9) The patient with recurrence lesion invasive to carotid artery and to skin.
- (10) Patients with phenylketonuria.

RESULTS: We enrolled one patient and undertook BNCT during this period as follows:

Patient #1: 46 y.o. female
Recurrence of cancer of the external ear
Histology: squamous cell carcinoma
Effect: SD
SAE: none; dermatitis, Grade 2

CONCLUSION:

We will continue to accumulate the cases carefully to establish a safe and stable treatment of BNCT.

CO7-15 Anti-tumor evaluation of Gadolinium Neutron Capture Therapy through comparison of tumor size using with polymeric nanocarriers

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INTRODUCTION:

Neutron Capture Therapy(NCT) is a nonsurgical therapeutic modality for treating locally invasive malignant tumor. Basically, there are boron NCT and Gadolinium NCT. Considering the possibility of MRI-guided GdNCT because gadolinium compound is a kind of MRI contrast agent [1], we focused on GdNCT. However, clinical Gd-chelates lack high and selective accumulation in tumors for electing safe and potent GdNCT [2].

Recently, nanoscale drug becomes more and more popular because it can promote the accumulation of Gd agents in tumor through the enhanced effect of permeability and retention (EPR). Therefore, we built a series of nanocarriers to improve the accumulation in tumor and evaluated its antitumor effect through the comparison of tumor size.

EXPERIMENTS:

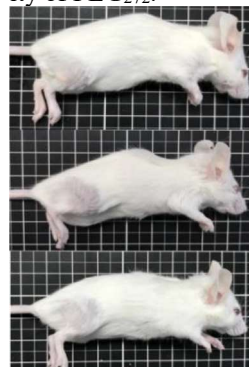
First of all, a series of nanocarriers based on poly(aspartic acid) (P(Asp)) were developed and they were modified with poly(ethylene glycol) (PEG) chains in order to have different molecular weight (Mw). And then, through the introduction of Gd-DOTA, PEG₂₇₂(PEG₂₇₂-P(Asp-Gd-DOTA)) and PEG₄₅₄(PEG₄₅₄-P(Asp-Gd-DOTA)) were made as the final products.

After 24h injection into colon 26 tumor-bearing mice with PEG₂₇₂ and PEG₄₅₄, respectively, the tumor-bearing mice received neutron irradiation 60 minutes at Nuclear Reactor Facility of Kyoto Univ Institute for Integrated Radiation & Nuclear Science with average neutron fluence of 2.0×10^{12} n/cm². Moreover, considering the influence of irradiation, we also set the mice injected same samples but without receiving irradiation as controls groups.

After almost one-month observation, the situation of all mice was recorded and the conclusion about antitumor effect was showed below according to the tumor size comparison photos.

RESULTS:

From the photo of tumor size after one-month observation, we can easily know that compared with the control group, tumor growth was suppressed with the injection of samples and according to the comparison in the control group, the suppression worked not only through the irradiation, but the influence of samples. Especially in the PEG₂₇₂ group, the tumor almost disappeared after irradiation which indicated the excellent tumor suppression ability of PEG₂₇₂.



With irradiation(Left)



Without irradiation(Right)

PEG₂₇₂ group



With irradiation(Left)



Without irradiation(Right)

PEG₄₅₄ group



With irradiation(Left)



Without irradiation(Right)

Control group

Table1. Tumor growth suppression by GdNCT using PEG₂₇₂ / PEG₄₅₄

REFERENCES:

- [1] A. Narmani *et al.*, J. Drug Deliv. Sci. Technol., **2018**, 44, 457-466.
[2] H. Tokumitsu *et al.*, Pharm. Res., 1999, 16, 1830-1835.

CO7-16 Accelerated deterioration assessment of SOF detector under high neutron flux environment

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INTRODUCTION: In the conventional BNCT, thermal neutron flux and thermal neutron fluence during treatment could not be measured in real time because gold wire activation was used to evaluate thermal neutron fluence. Therefore, we developed a detector (SOF detector; Scintillator with Optical Fiber Detector) with a plastic scintillator attached to the tip of the optical fiber, tried real-time measurement of thermal neutron flux in neutron capture therapy, and got good results. The long-term stability of the SOF detector and the wide measurement dynamic range (linearity of 10^4 to 10^{10} n/cm²/s) have been confirmed in previous collaborative experiments. [1,2] However, signal degradation of SOF detector in long-term exposure was reported [3]. The signal degradation might not be a significant problem in case that calibration can be performed before use. However, signal degradation greatly affects measurement accuracy in case of long-term monitoring because calibration prior to use is difficult. In previous experiment performed at last academic year, we tried to identify the causative substance of signal deterioration of the material in the SOF probe, however, it was difficult to specify the caused material because the amount of signal deterioration was not sufficiently large at Heavy Water Neutron Irradiation Facility (HWNIF). Therefore, we conducted a deterioration characteristic assessment in a high flux environment.

EXPERIMENTS: The experimental geometry is shown in Fig. 1. The Slant exposure tube (SET) facility SET of KUR was used for irradiation. The SOF detector probes were arranged at about 50 cm above from the bottom of Slant hole where estimated thermal neutron flux was 4.68×10^{10} n/cm²/s with 5 MW operation. The combinations of neutron converter and reflectors contained in the irradiated probes are shown in Table 1. All probes used BC490 as a plastic scintillator, and Probes 1 and 2 were mixed with ⁶LiF as a neutron converter. Moreover, BC642 (PTFE Reflector Tape) and BC620 (Reflector paint) were used as a reflective material.

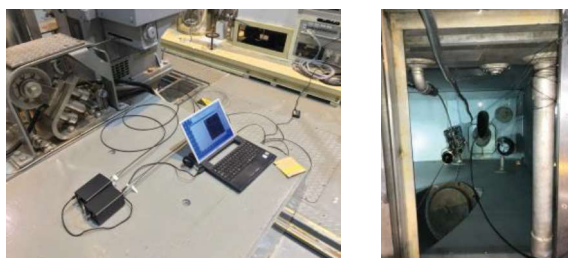
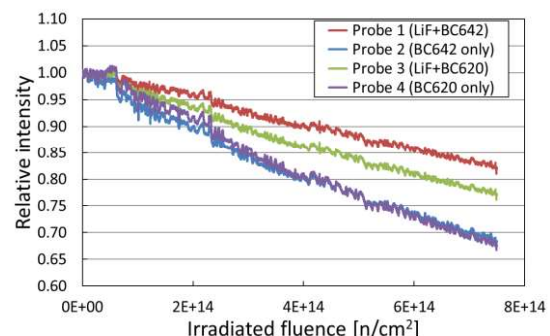


Fig. 1. Irradiation geometry for on-line assessment of deterioration characteristics at Slant exposure tube.

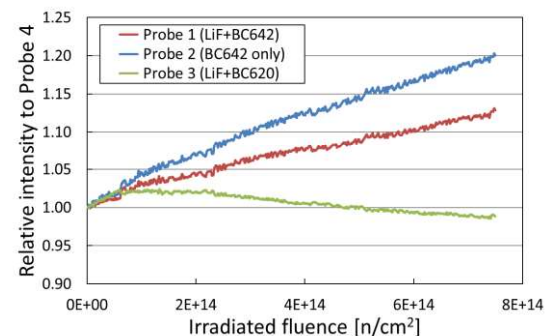
Table 1 Probe characteristics.

Probe	Neutron conv.	Reflector	Slope [%/n·cm ⁻²]
1	⁶ LiF	BC642	-2.38×10^{-14}
2	-	BC642	-4.55×10^{-14}
3	⁶ LiF	BC620	-3.26×10^{-14}
4	-	BC620	-4.53×10^{-14}

RESULTS: Figure 2 shows the relative change for each probe from the initial signal intensity at irradiation start. From Fig. 2, the signal intensity is greatly attenuated with the irradiation. The slope of signal deterioration assuming attenuated linearly was shown in Table 2. With respect to the thermal neutron dose of 10^{14} n/cm², it was confirmed that the probe mixed with the neutron converter showed ~3% attenuation, and the probe containing no neutron converter had 4.5% attenuation. Usually, neutron fluence of $\sim 10^{13}$ n/cm² is irradiated in BNCT treatment, so it is estimated that signal deterioration during treatment is less than 0.5%. On the other hand, according to the report of Nakamura *et al.*, the deterioration of the plastic optical fiber is considered to be a major factor because the damage caused by irradiation was reduced by constructing SOF detector probe with a quartz optical fiber.[4] Our result that the signal deterioration was confirmed regardless of the presence or absence of the neutron converter is consistent with the report of Nakamura *et al.*



(a) Normalized at initial signal intensity.



(b) Normalized with probe #4.

Fig. 2. Irradiation geometry for on-line assessment of deterioration characteristics.

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