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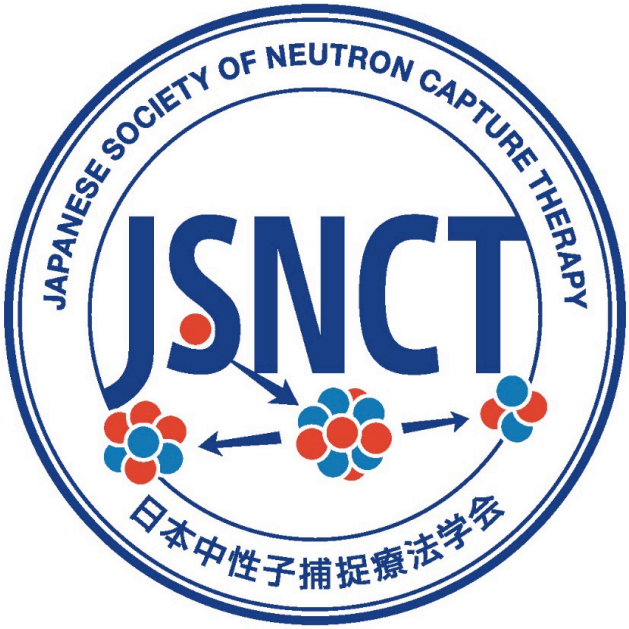

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Mitsuko Masutani
Chief Editor of NCT letter
Graduate School of Biomedical Sciences, Nagasaki University

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● *Preface*

Request for Participation in the Joint Usage Research Project, Advanced Nuclear Science Research Institute, Kyoto University

Minoru Suzuki
President, Japanese Society of Neutron Capture Therapy
Professor, Particle Radiation Oncology Research Center,
Institute for Integrated Radiation and Nuclear Science,
Kyoto University

Thanks to the efforts of Dr. Itsuro Kato, the former Editor-in-Chief of NCT letter, and Dr. Mitsuko Masutani, his successor, as well as the cooperation of many doctors, we are pleased to publish NCT letter No. 8.

As mentioned in the preface of NCT letter No. 7, accelerator-based boron neutron capture therapy (BNCT) for head and neck cancer has been started at two medical institutions. Needless to say, the clinical study of BNCT using a research reactor is the cornerstone of the initiation of BNCT at these institutions. I have been involved in many clinical studies at the Kyoto University Research Reactor (KUR) in the Institute for Integrated Radiation and Nuclear Science, Kyoto University, in collaboration with doctors from medical institutions. The curtain was pulled back on BNCT clinical studies at KUR with the start of accelerator-based BNCT at medical institutions in FY2019, and the future development of BNCT medicine was handed over from the research reactor to medical institutions with accelerator-based BNCT irradiation systems.

I would like to discuss the role of KUR after the completion of clinical studies of BNCT based on the current status of the Combined Research Center and from the standpoint of conducting collaborative research with many researchers. The special feature of BNCT research is that it requires neutrons as a proof of concept. The KUR neutron source is the only one that can provide a sufficient number of neutrons for BNCT research from the standpoint of the academia. Conversely, the start of BNCT treatment at medical institutions will give rise not only to research on the development of new boron drugs but also to many other research subjects, such as bridge research to connect the results of research from basic to clinical practice, and new research subjects that will be fed back to basic research from the results of the BNCT clinical research at medical institutions.

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It is important to broaden the scope of BNCT research to allow a smooth transition to BNCT research using accelerator-based neutron sources after the end of the KUR Collaboration in Japan. The existence of more research subjects and BNCT researchers will lead to the expansion of the use of not only the cyclotron accelerator-based BNCT irradiation system at Institute for Integrated Radiation and Nuclear Science but also the accelerator-based BNCT irradiation systems that are under demonstration studies at several sites in Japan. In this respect, I believe that the KUR, which only has 5 years remaining, has an extremely important role to play. Above all, we strongly hope that the number of young researchers entering BNCT research will increase. It is, after all, young researchers who can conduct many BNCT studies from unique viewpoints due to their flexible imagination. The number of biological experiments conducted in FY2020 is expected to increase to 1,000 in FY2021. In FY2021, 180 experiments were conducted from June to December (18 weeks of operation), and 10 biological experiments were conducted on average per week of operation. Even if the number of experiments increases, we will cope with it by improving the efficiency of various irradiation methods that we have been using.

In the Institute for Integrated Radiation and Nuclear Science (KURNS), there is the Center for Particle Beam Oncology, of which I am the director, and to which faculty members in the fields of particle beam oncology and particle beam medical physics belong. One of the duties of the center's faculty members is to promote joint research. In the last fiscal year and this fiscal year, due to the spread of the novel coronavirus, many experiments have been conducted by the faculty members of the KURNS on behalf of those who are unable to come to the center due to travel restrictions. The KURNS faculty members are also responsible for observation of mice after irradiation, colony fixation, mailing, etc. Please do not hesitate to contact us for consultation. The remaining 5 years of the project, and since the current year's joint use is nearing its end, the actual period of use is 4 years. In order for accelerator-based neutron sources to inherit the mantle of Japanese BNCT therapies, which are already world-leading in their scope, it is extremely important for us to achieve many research results using the remaining lifespan of the KUR. Members of the society, if you are interested in BNCT research but are unsure of how to approach performing the research itself, please visit the website of the Particle Radiation Oncology Research Center. Contact information is available on the members' introduction page.

Thank you for your continued support and cooperation.

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● *Special Articles*

Medical physics research in BNCT

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Kyoto University

Medical physics research is critical to BNCT and has played a role in the proper "generation, control, detection, and evaluation" of neutrons. From the time clinical research on BNCT began in the United States in 1951 until the 1990s, thermal neutron beams, in which fission neutrons from research reactors were decelerated to the thermal neutron energy region, were used for treatment. Since thermal neutrons cause an absorption reaction with hydrogen, treatment was performed for surface malignant melanoma or brain tumors in craniotomies.

In the 1990s, in research reactors around the world, there was a growing need to enable treatment at deeper depths, and it became possible to extract controlled epithermal energy, which is more energetic than thermal neutrons. Since neutrons have no electric charge, several materials with a nuclear reaction cross section with high scattering moderating ability and low absorption are used for the control of neutron energy. This is applicable not only to reactor neutron sources but also to accelerator neutron sources. In addition, accelerator neutron sources can produce neutrons in a wide variety of ways, depending on the combination of charged particle energy and neutron-producing target. Neutron generation and control are closely related, and it is important to design from the viewpoint of medical physics with clinical considerations. Accelerator neutron source systems are described in detail in NCT letter No. 7.

Since generated and controlled neutrons have a wide energy range from 10^{-8} to several tens of MeV, proper detection of neutron energy spectra is necessary for clinical applications. It is difficult to measure 9 orders of magnitude of neutron energy at once because the interaction between neutrons and materials is complex and the type of interaction differs for each energy. In addition, the neutron intensity in the irradiation field of BNCT ranges from 10^6 to 10^9 (n/cm^2 /s); thus, survey meters and other instruments normally used in radiation protection are not applicable.

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Thermal neutrons are measured indirectly by measuring gamma rays emitted from radionuclides produced by the capture reaction. We have followed the neutron detection method used by the nuclear reactor neutron source. In contrast, a new detection method is being developed using scintillators containing ^{10}B and ^{6}Li, which have high absorption cross sections for thermal neutrons, to enable real-time measurements. Fast neutrons are also difficult to measure directly, and methods using activation of metal foils sensitive to energies higher than a certain energy and Bonner spheres to detect thermal neutrons by moderating them with a polyethylene sphere are being developed for the BNCT irradiation field.

Measurement of epithermal neutrons used in therapy is more difficult, and we have confirmed the validity by measuring the thermal neutron flux distribution when irradiated in a water phantom. Thermal to fast neutron detection requires a combined evaluation with calculations such as Monte Carlo simulations.

Monte Carlo simulations are also used in treatment planning, where computed tomography (CT) and magnetic resonance imaging (MRI) medical images are modeled as voxels and neutron energy spectra are calculated for each voxel by performing neutron transport calculations. Each energy is converted to a dose, and the equivalent X-ray dose is evaluated considering the biological effects. The Monte Carlo simulation is computationally time-consuming; therefore, it is required to be completed in the same amount of time as the treatment planning for X-ray therapy, and research to solve this problem is underway. It is expected that AI and machine learning, which are incorporated into the research of X-ray therapy, can also be applied to BNCT.

As described above, medical physics research at BNCT has been conducted with the theme of appropriate "generation, control, detection, and evaluation" of neutrons. It is also important to evaluate the cell-killing effect of BNCT because the effect depends on the microscopic distribution of boron. With the development of computational science, it has become possible to evaluate the boron distribution in the cellular dose and to simulate the biological effects computationally. Furthermore, it has been proposed that the boron concentration during treatment can be measured by detecting prompt gamma rays emitted by the reaction of thermal neutrons with ^{10}B at BNCT, which is expected to be a necessary technique for evaluating the treatment effect.

We believe it is important to link the above medical physics research to clinical practice. BNCT with insurance coverage for unresectable locally advanced or locally recurrent head and neck cancer has been started at medical institutions. Medical physics research in clinical practice includes items related to optimization of dose distribution

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and quality and accuracy control of equipment. It is expected that more and more medical physics research will be performed in clinical practice in the future.

The Institute for Integrated Radiation and Nuclear Science, Kyoto University has two neutron source facilities, a research reactor and an accelerator neutron source, both unique in the world, and is promoting research and development of BNCT. The Department of Particle Radiation Medical Physics, Particle Radiation Oncology Center (PBOCC) has succeeded to the BNCT medical physics research that has been conducted by Dr. Akira Maruhashi, and we hope to contribute to the spread and development of BNCT by incorporating new knowledge.

After approval of antineoplastic agent "Steboronin® Bag for Intravenous Infusion 9000 mg/300 mL"

Tomoyuki Asano
Chairman & CEO, Stella Pharma Corporation

Many patients with head and neck cancer wish to preserve functions such as speech, swallowing, chewing, and breathing. Thus, it is hoped that medical technology can enable us to shrink only the tumor in question, without damaging surrounding normal cells, and thereby maintain the patient's quality of life.

Therefore, in the treatment of head and neck cancer, efforts are made to minimize functional disability after treatment as well as to cure the disease. From this perspective, nonsurgical treatment is chosen when significant postoperative functional disability is expected.

BNCT is expected to be a new radiotherapy for head and neck cancer that can also be re-irradiated, since its principle allows high doses to be given to tumor cells with minimal effect on surrounding normal cells.

Based on the results of clinical trials conducted in Japan to meet these expectations, the drug received manufacturing and marketing approval in Japan in March 2020 for the indication of "unresectable locally advanced or locally recurrent head and neck cancer," ahead of any other country in the world.

Below are the clinical results for the approved Steboronin®.

Phase II clinical study in Japan (JHN002 study)[(1)]

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In 21 patients with (1) unresectable locally recurrent squamous cell carcinoma of the head and neck following chemoradiation or radiation therapy or (2) unresectable non-squamous cell carcinoma of the head and neck, 500 mg/kg of the drug was administered intravenously at 200 mg/kg/h for the first 2 h and 100 mg/kg/h thereafter. Patients were also irradiated with a single neutron dose of 12 Gy-Eq to the oral, pharyngeal, or laryngeal mucosa for up to 60 min starting 2 h after the start of Borofalan (^{10}B) administration. The primary endpoint of response rate (the sum of complete and partial responses) by central administration (RESIST v1.1) was 71.4% (90% confidence interval: 51.3–86.8%).

Regarding safety, brain abscess was observed in one patient (4.8%) as a serious adverse event during the observation period of the JHN002 study (up to 90 days after BNCT); 16 patients (76.2%) had grade 3 or higher adverse events including the aforementioned serious adverse events: increased amylase, lymphocytopenia in one patient (4.8%), decreased lymphocyte count in one patient (4.8%), stomatitis in one case (4.8%), brain abscess in one case (4.8%), and radiation skin damage in one case (4.8%).

In the JHN002 study, relatively common adverse events of BNCT included thirst, parotitis, sialadenitis, nausea, stomatitis, vomiting, fatigue, conjunctivitis, increased amylase, decreased appetite, dysgeusia, and alopecia. These events reported as adverse reactions to BNCT were considered general radiation injury or irradiation site-dependent events. Although "hematuria" was reported as an adverse reaction to BNCT in the domestic Phase I study, its occurrence was considered to have decreased after the JHN002 study because fluid loading with infusion was recommended. Therefore, the package insert “8. Important Basic Precautions” states “Crystalluria may occur; therefore, urinary drainage should be encouraged by administering intravenous fluids as necessary after completion of treatment. The following is a list of the important basic precautions.”

Based on the results of the above-mentioned clinical trials in Japan, BNCT using this drug is expected to have a tumor reduction effect not seen in existing therapies as a novel treatment for patients with unresectable locally advanced or locally recurrent head and neck cancer, and is considered to meet the medical needs and provide a new treatment option. The following are the [Use and Dosage] and <Use and dosage precautions > specified in the package insert.

[Use and Dosage]

The usual adult dose of Borofalan (^{10}B) is 200 mg/kg per hour intravenously for 2 h. Neutron irradiation of the lesion site is then initiated, and Borofalan (^{10}B) is given intravenously at a rate of 100 mg/kg per hour during irradiation.

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<Use and dosage precautions>

- The efficacy and safety of concomitant use with other antineoplastic agents have not been established.
- The neutron irradiation device manufactured by Sumitomo Heavy Industries, Ltd., shall be used to irradiate neutrons.

This drug was designated by the Ministry of Health, Labour and Welfare (MHLW) on February 28, 2017, as a drug subject to the "Pioneer Review Designation System."

This is proof that the Ministry of Health, Labour, and Welfare has recognized BNCT as an innovative medical technology for life-threatening diseases for which there is no effective treatment and as a medical industry that can keep Japan at the forefront of the world.

We will never betray these expectations, and we will work hard to remain the best globally.

【Reference】

(1) Hirose K, et al. Boron neutron capture therapy using cyclotron-based epithermal neutron source and borofalan (^{10}B) for recurrent or locally advanced head and neck cancer (JHN002) : An open-label phase Ⅱ trial.

Initiatives for research on the expansion of BNCT indications for companion animals

Minoru Suzuki
Professor, Particle Radiation Oncology Research Center,
Institute for Integrated Radiation and Nuclear Science,
Kyoto University

The Center for Particle Radiation Oncology, Institute for Integrated Radiation and Nuclear Science, Kyoto University has concluded a joint research agreement with the Veterinary Clinical Center, Osaka Prefecture University, and has been working on the expansion of the indications of BNCT for companion animals.

I would like to discuss the importance of research on extending BNCT indications for companion animals and the efforts of this research at the Institute for Integrated Radiation and Nuclear Science. The importance of this research is based on the

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principle of "One medicine, One health," which means that both "human medicine" and "animal veterinary medicine" are medicine in common, and the findings from this research will be applied to human BNCT research. This is a bidirectional undertaking that will benefit both fields. An example is my basic research on whole-organ BNCT. In human BNCT for the liver and lungs, it is impossible to irradiate the entire organ uniformly with neutrons. I have been conducting normal tissue studies of BNCT on the liver and lungs using mice and rats, and it is important to use companion animals such as dogs and cats, which bridge the gap between humans and rodents. As for actual veterinary medicine, I believe that bone and soft tissue sarcomas, head and neck cancers, and malignant brain tumors, for which clinical studies have been conducted in humans as therapeutic targets at the Institute for Integrated Radiation and Nuclear Science, may be candidates for BNCT. Conversely, if the size of dogs and cats is small, neutrons can be irradiated relatively uniformly to all target organs by whole-liver and whole-lung irradiation, and patients with multiple lung metastatic tumors and multiple liver metastatic tumors that are not eligible for radiation therapy in human treatment may become eligible for BNCT treatment. In the field of veterinary medicine, BNCT may provide a new treatment method for multiple metastatic tumors, and in the field of human medicine, BNCT may enable long-term observation of the effects of BNCT on normal liver and normal lung and may provide important knowledge on tumors in the human trunk.

As part of this research initiative at the Institute for Integrated Radiation and Nuclear Science, research meetings have been held in FY 2019 and FY 2020. The FY 2020 meeting was held remotely on March 4, 2021 due to the coronavirus pandemic. Dr. Amanda Schwint, who has conducted BNCT of companion animals from Argentina using a research reactor, gave an educational lecture at this meeting. We are planning to hold another workshop in FY2021 as a specialized research group of RRI. In addition, "Basic Research for Expanding Adaptation of BNCT to Companion Animals" has been adopted as a 3-year project research from FY2022, and several research themes have been applied for this project.

We would like to report many research results using the neutron source at KUR so that as many veterinary researchers as possible can participate in this research.

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● *Academic meeting Reports*

Report on the 17th Annual Meeting of the Japanese Society for Neutron Capture Therapy

Jun Itami
President of 17th JNCT
Director, Radiation Therapy Center,
Shin Matsudo Central General Hospital

The 17th Annual Meeting of the Japanese Society for Neutron Capture Therapy was held on July 10–11, 2021, at the KKR Hotel Atami in Atami City, Japan, using a mix of live and web-based presentations. In 2021, the situation was similar, but considering the rapid development of accelerator-based BNCT in Japan, it was considered essential to hold an academic conference, even if it was via the web. We had planned to hold a live conference in the gap between the emergency measures to prevent the epidemic, but a mudslide occurred in Atami, where the conference was to be held, on July 3, 2021, and it was doubtful whether we could hold the conference in Atami considering the disaster. However, when we contacted the city of Atami, we were told that the area around the KKR Hotel Atami, the venue of the conference, was perfectly safe and that they would be happy to host the conference. We would like to thank Dr. Hiroshi Igaki and Dr. Tetsushi Nakamura of the Department of Radiotherapy, National Cancer Center Hospital, and other doctors who worked day and night as the conference secretariat. I would like to express my deepest gratitude to them.

The theme of the conference was "Neutron Capture Therapy from Japan to the World." The clinical practice of accelerator-based BNCT is now almost exclusively performed in Japan. In the conventional reactor BNCT, the number of patients treated is limited and it is difficult to enroll a large number of patients in clinical trials. I am a newcomer to this society, but I have learned a lot from the reports of the wonderful researchers who have pioneered a new field and are full of spirit to go forward on an unprecedented path at the annual meeting. It is truly "don't do the same thing as others." However, once the topic shifts to clinical practice, it is necessary to increase the number of patients and clear the question of whether BNCT is statistically significantly superior. It is necessary to earn the number of patients with the same treatment by doing "the same thing as others." It seems that the perspective that was a little lacking in the

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conventional society is also important. To expand the indications for BNCT's insurance medical treatment in the future, it is necessary to show the superiority of BNCT statistically. Westerners appear to be quite good at this kind of thing, and Japanese people are relatively weak in this area. Indeed, I myself am completely unfamiliar with this.

In Japan, the cyclotron-based BNCT accelerator and treatment planning system developed by Sumitomo Heavy Industries, Ltd., and Stella Pharma Corporation's boronophenylalanine (BPA) is indicated for some head and neck cancers. In contrast, the National Cancer Center Hospital is using CICS's linear accelerator-based BNCT accelerator and Stella Pharma Corporation's BPA are used for malignant melanoma of the skin and vascular sarcoma. If the current situation continues, each accelerator will have to expand the range of indications for the same disease with separate trials. If BNCT can be covered by insurance on a disease-by-disease basis, it will be possible to treat patients with both accelerators, which will be greatly beneficial.

Considering this, we invited Dr. Kiyoto Nakai, then Director of the Pharmaceutical Safety Division, Pharmaceuticals and Consumer Health Bureau, MHLW, and Dr. Kensuke Ishii, Director of the First Medical Device Review Division, Pharmaceuticals and Medical Devices Agency, to give valuable presentations at this conference. The meeting was very well attended. We, as an academic society, would like to clarify the basic requirements for BNCT accelerators as soon as possible, and if these requirements are met, regardless of the accelerator vendor, the regulatory approval should be obtained as soon as possible. We now know that there is a way to be able to claim reimbursement for BNCT-indicated diseases. It is important for us to move forward by concentrating the power of our society more and more.

In the general abstracts, there were reports on clinical results of accelerator-based BNCT, development of new BNCT drugs,

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improvement of administration methods, tolerable dose of normal tissues, real-time measurement method of thermal neutrons, etc. Many of the topics were discussed in more depth than those at the international conference, and I felt deeply that this is a technology that is still developing in Japan. We had a great time.

We hope that the conference members who came to the conference venue in Atami enjoyed the hot spring while looking at the sea of Atami. Next year, Dr. Hiroaki Kumada of Tsukuba University will hold the conference at Tsukuba International Congress Center from October 29 to 30. We hope to see and talk with you all directly at that time.

Thank you so much for this opportunity.

● ***Awardees***

The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Prizes for Science and Technology, 2021

2021 Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology Science and Technology Prize

Koji Ono
Professor, Kansai BNCT Joint Clinical Institute,
Osaka Medical and Pharmaceutical University

In April last year, we received an award from the Minister of Education, Culture, Sports, Science and Technology (MEXT) for the practical application of the world's first accelerator-based BNCT system. We would have attended the award ceremony at the MEXT, but due to the coronavirus disaster, the ceremony was held only with some representatives of the Tokyo group, and we attended online. I am sure that all of you are aware that the achievements of the awardees are not only due to myself, Dr. Suzuki & Dr. Tanaka (Institute for Integrated Radiation and Nuclear Science, Kyoto University), Dr. Mitsumoto (Sumitomo Heavy Industries, Ltd.), and Dr. Asano (Stella Pharma Corporation). In the field of accelerator irradiation systems, the contributions of Akira

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Maruhashi (Professor Emeritus of Kyoto University, Institute for Integrated Radiation and Nuclear Science) and Takemi Sato (formerly of Sumitomo Heavy Industries, Ltd.) have been extremely significant. The same is true of Mitsunori Kirihata (Professor Emeritus of Osaka Prefecture University), who has contributed greatly to the development of boron-based drugs. Concurrently, many doctors and researchers who were involved in clinical trials, which are indispensable for clinical application, are also considered to have made great contributions. The collaboration of these many people has resulted in an achievement worthy of commendation.

In retrospect, we conducted clinical research on BNCT using the Kyoto University Reactor (KUR) and L-4-boronophylalanine (L-BPA) fructose complex solution for many years, but it was impossible to make BNCT an approved medicine as long as a nuclear reactor was used as the neutron source. At the beginning of this century, we made a world-leading leap forward in clinical research, and the momentum to make BNCT an approved medical treatment grew among our collaborators. Therefore, we have been developing an accelerator neutron source that can replace the research reactor as an approved medical device, and a long-term stable BPA preparation that can replace the fructose complex solution.

We designed an accelerator neutron source based on the results of medical physics accumulated in the research using KUR and our past achievements in cyclotron development. The cyclotron accelerates 1 mA protons to 30 MeV, and the target is made of beryllium for heat and proton resistance, which enables us to obtain a stable beam of epithermal neutrons with a flux density 1.5 times higher than that of the Kyoto University reactor. The moderator system was optimized so that the most frequent energy of the produced neutrons is 10 keV, which is higher than that of the Kyoto University reactor.

Conventional L-BPA fructose complex solutions of boron drugs have instability due to the Maillard reaction caused by the amino and carbonyl groups, which is a problem if they are to be used as drugs for which stable supply is essential. In this development, the stability problem was solved by employing D-sorbitol as a dissolution aid, and combined with our original boron-10 isotope enrichment technology, it became possible to create a boron drug for BNCT with low systemic toxicity and high accumulation in tumor tissues.

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We conducted physical characterization studies of the treatment system and pharmacological and toxicological studies of the boron drug prior to conducting clinical trials, including the world's first accelerator-based BNCT phase I clinical trial for recurrent malignant glioma in 2012 and a phase I clinical trial for inoperable locally advanced and recurrent head and neck cancer in 2014. We initiated a phase II clinical trial in 2016. The response rate for head and neck cancer reached 71.4%, and the frequency and severity of side effects were confirmed to be comparable to those of existing radiotherapy. In 2017, the Ministry of Health, Labour and Welfare designated the drug for the Pioneer Review Designation System, and an application for approval will be submitted in 2019. In 2020 NeuCure® system and NeuCure® Dose Engine, a BNCT dose calculation program, received manufacturing and marketing approval as medical devices, and on March 25 of the same year, Steboronin® intravenous infusion bag, a boron drug for BNCT, also received manufacturing and marketing approval as a drug, and on May 20 of the same year, the world's first BNCT drug is now on sale as a drug.

Fig. 1 Medals of commendation

The BNCT treatment system NeuCure® has been installed at the South Tohoku BNCT Research Center and the Kansai BNCT Medical Center of Osaka Medical and Pharmaceutical University, and the world's first insured treatment of BNCT using Steboronin® started in June 2020.

These and other achievements were achieved ahead of the world through purely domestic technology and collaboration between industry, government, and academia, and are expected to contribute to medical care not only in Japan but worldwide. However, the PMDA has judged that the clinical trial results of BNCT for malignant glioma, which has led the clinical research, have not yet been scientifically proven to be effective, and are in the process of reanalyzing and reevaluating the data. From another scientific point of view, even though neutrons are used, BNCT is not yet fully recognized as one of radiotherapy. This is reflected in the fact that the relationship between tumor dose and efficacy is not yet clear. The incorporation of FBPA-PET into medical practice is indispensable to solve this problem, and the early initiation of clinical trials of FBPA-PET is highly desirable. Optimization of neutron energy and enhancement of neutron intensity (flux density) are also important issues. Research on

the effects of BNCT on normal tissues with tumors is also essential to expand the application of BNCT to new tumor types. It is clear that a further major breakthrough will depend on the development of new boron drugs that far surpass BPA.

By reporting on the Minister's Commendation, I hope that JSNCT members would continue their efforts in their respective fields for the further development of BNCT.

● *Awardees of BNCT related Conferences or Meetings*

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

Translational research of the therapeutic application of boron neutron capture therapy (BNCT) to primary central nervous system lymphoma (PCNSL)

Kohei Yoshimura, et al.
Department of Neurosurgery,
Kansai BNCT Medical Center,
Osaka Medical and Pharmaceutical University

BNCT is a particle beam therapy that selectively destroys tumor cells using alpha particles emitted by the nuclear reaction of non-radioactive boron atoms ^{10}B and neutrons (^{10}B[n,alpha]^{7} Li). Primary central nervous system lymphoma (PCNSL) is a malignant brain tumor classified as World Health Organization grade IV. High-dose methotrexate and whole brain radiation therapy are recommended for treatment. PCNSL is highly responsive to initial therapy but relapses after successful treatment, and prognosis is poor with few treatment options for relapse. Therefore, there is a need to develop novel therapies for PCNSL and potential therapies that can be used at relapse. We performed a basic study of BNCT, which has already been clinically applied to malignant glioma, a similar intracranial malignancy, to evaluate its potential as a new treatment option for PCNSL, including recurrent cases, by taking advantage of its high cell selectivity.

In an in vitro study, boron accumulation after exposure to boronophenylalanine (BPA) was evaluated using two types of human-derived lymphoma cells, Raji and RL, to assess the effect of BNCT with BPA on lymphoma cells. BPA was administered to

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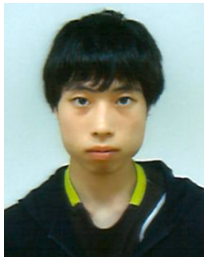
transplanted nude mice (mouse brain tumor model), and boron concentrations in each organ and tumor were measured. Neutron irradiation experiments were also performed on the mouse brain tumor model to evaluate the therapeutic effect of BNCT on the mouse brain tumor model in terms of survival time.
Lymphoma cells demonstrated high boron uptake capacity. In vivo distribution experiments using a mouse brain tumor model confirmed tumor-selective boron accumulation. In the first neutron irradiation experiment in the mouse CNSL model, the survival time of the BNCT group was short because the equivalent dose to the oral mucosa was high and the mucosal damage caused early death. The survival benefit of BNCT was shown to be prolonged when neutron irradiation experiments with dose reduction were designed and conducted. These results indicate that BNCT is effective in malignant lymphoma. Based on the results of this study, we are now conducting additional experiments to apply BNCT to PCNSL in clinical practice.
Finally, I would like to express my sincere appreciation to Dr. Shinji Kawabata for his support for this presentation; Dr. Jun Itami, the conference director, who selected this presentation for the Best Presentation Award; all the members of the conference secretariat and the judges; and the authors of the NCT letter for their kind cooperation in this project. I would like to thank Dr. Mitsuko Masutani for giving me the opportunity to write this article.

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

Poly(vinyl alcohol) enhancing therapeutic effects of D-4-boronophenylalanine



Kakeru Konarita, et al.

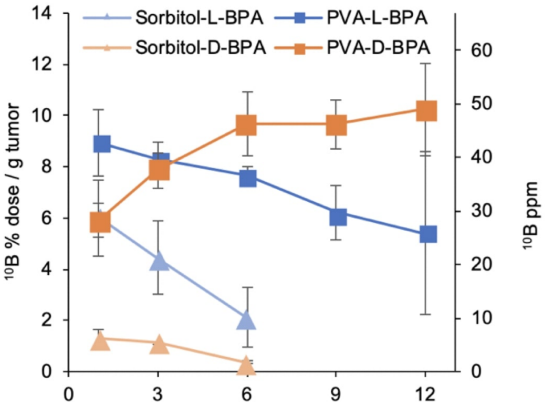
Institute of Innovative Research, Tokyo Institute of Technology

In 2020, our laboratory reported that the addition of polyvinyl alcohol (PVA) to L-boronophenylalanine (L- BPA) can improve BPA's tumor accumulation and retention capacities, thereby maintaining high intratumoral boron concentration during thermal neutron irradiation and significantly enhancing the therapeutic effect of L- BPA [***Science Advances*** **6**, eaaz1722 (2020)]. In this study, we focused on the fact that D-boronophenylalanine (D-BPA), an enantiomer of L-BPA, has higher selectivity for

LAT1 than L-BPA, and developed PVA-D- BPA, in which D-BPA is loaded on PVA, and investigated its *in vitro* and *in vivo* behavior.

First, we evaluated the uptake and intracellular retention of sorbitol-L/D-BPA and PVA-L/D-BPA in human pancreatic cancer cells. Sorbitol-D-BPA had a significantly lower uptake efficiency than sorbitol-L-BPA. This may be due to the fact that D-BPA was selectively taken up by LAT1, whereas L-BPA was also taken up by other LAT2 and $ATB^{0,+}$. However, D-BPA uptake was enhanced by the complex formation with PVA. In addition, we found that D-BPA showed much longer intracellular retention than L-BPA. This may be because LAT1 has an intracellular transport function that is permissive for many neutral large amino acid compounds including D-BPA, and this property does not work for D-BPA in extracellular transport.

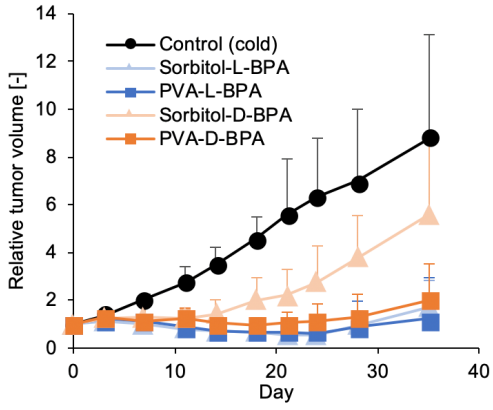
A



B

Time course	PVA-L-BPA	PVA-D-BPA
1	1.8 ± 0.3	4.3 ± 0.4
3	1.9 ± 0.2	3.5 ± 0.2
6	1.9 ± 0.1	3.2 ± 0.2
9	1.4 ± 0.3	2.9 ± 0.04
12	1.9 ± 0.3	2.8 ± 0.7

A



B

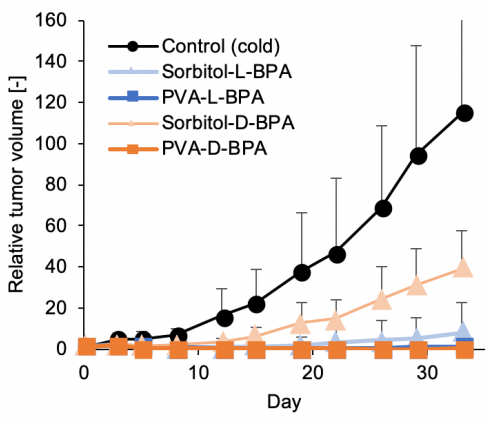


Figure 1. (A) Accumulation of BPA in tumors in a mouse subcutaneous pancreatic cancer model. (B) Tumor to muscle tissue ratio (T/N ratio) of PVA-L/D-BPA.
Figure 2. Anti-tumor effect. (A) Subcutaneous pancreatic cancer model. (B) Subcutaneous colon cancer model. Thermal neutrons were irradiated 3 h after intravenous injection.

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Tumor accumulation of these samples was then evaluated in a mouse subcutaneous pancreatic cancer model (Figure 1). Sorbitol-D-BPA hardly accumulated, but D-BPA significantly improved its tumor accumulation by forming a complex with PVA, and showed higher boron concentration and long-term retention than PVA-L-BPA. In addition, PVA-D-BPA accumulated less in muscle tissue than PVA-L-BPA, probably due to its higher LAT1 specificity, and improved the T/N ratio. Moreover, PVA-D-BPA showed superior BNCT effect on subcutaneous tumors (Figure 2).

D-BPA by itself has a lower uptake efficiency than L-BPA at first glance and is not expected to have excellent tumor accumulation *in vivo*. However, D-BPA was shown to exhibit its true value by forming a complex with PVA, suggesting that D-BPA may even have a therapeutic potential greater than PVA-L-BPA for LAT1-targeted cancer therapy. However, the mechanism by which the complex formation between BPA and PVA increases BPA uptake remains unclear, and we intend to clarify this mechanism in more detail in the future.

Finally, I would like to express my sincere gratitude to Dr. Jun Itami, the conference chairman, Dr. Minoru Suzuki, the president of the society, for selecting this presentation for the Best Presentation Award, and Dr. Mitsuko Masutani for giving me the opportunity to write this paper. We also thank Dr. Hiroyuki Nakamura for his great advice and Dr. Yoshinori Sakurai, Dr. Hiroki Tanaka, and Dr. Takushi Takada for their special support in neutron irradiation.

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

Refining the CBE factor of BPA in the brain with malignant brain tumors

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Osaka Medical and Pharmaceutical University

The biological effects of normal particle therapy can be described by the product of the constant relative biological effectiveness (RBE) and the physical dose. However, in BNCT, the microdistribution of boron changes depending on the drug and the target tissue. Therefore, the biological effects of α particles and Li nuclei

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emitted by BNCR (boron-neutron capture reaction) cannot be calculated using a constant RBE. Instead of RBE, compound biological effectiveness (CBE) is used in BNCT. Currently, a value of approximately 1.35 is used worldwide for clinical studies and trials of brain tumors as the value for normal brain tissue. However, this value is calculated by physical dose based on the boron concentration in blood and is only a value obtained under specific experimental conditions without considering the boron concentration in normal brain. In 2016, co-author Ono reviewed several reports under various experimental conditions and found that CBE levels are significantly affected by boron concentration in normal brain tissue. Specifically, the value can be described by the formula (CBE = 0.32 + 1.65 · N / B) with the term of N / B (normal brain / blood blood) of boron concentration added (Journal of Radiation Research, Vol. 57, No. S1, 2016, pp. i83–i89). According to this formula, the CBE value of BPA for malignant brain tumors was reconsidered.

The BPA concentration for malignant brain tumors was substituted by the brain SUVmean obtained from FBPA-PET, and the blood BPA concentration was substituted by the SUVmean obtained from the cardiac pool. Brain SUVmean was 1.21 ± 0.27 and 1.65 ± 0.33 in the contralateral brain of the brain tumor and the ipsilateral brain bordering the tumor, respectively. The blood SUVmean was 1.12 ± 0.17. These values resulted in N(contralateral brain)/B(blood) = 1.07 ± 0.12 and N(ipsilateral brain)/B(blood) = 1.46 ± 0.26. CBE was calculated based on N/B in the contralateral brain (CBE=2.09) and N/B in the ipsilateral brain (CBE=2.73). In both ipsilateral and contralateral brains, the CBE values were much higher than the conventional value (1.35).

The currently used CBE value of 1.35 is likely to be underestimated as the bioequivalent dose to the normal brain. SUV values in the ipsilateral brain in contact with the tumor may be higher than in the contralateral brain due to partial destruction of the blood-brain-barrier by the tumor in addition to the effect of FBPA accumulated in infiltrating tumor cells. Furthermore, considering the dose effect of BPA in tumor cells mixed with normal brain cells, the SUV values may be even higher than the CBE estimated from the SUV values of the contralateral brain. More accurate calculation of CBE values and dose assessment for the normal brain are mandatory in the future.

Finally, I would like to express my deepest gratitude to Dr. Jun Itami, the Congress Director, who selected this presentation for the Best Presentation Award, to the judges, and to the NCT letter committee for the opportunity to write this paper.

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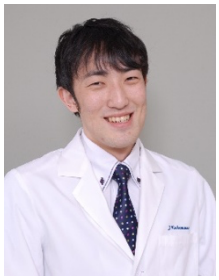
The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

Modeling of neutron production efficiency in an accelerator-based boron neutron capture therapy system with a lithium target and evaluation of its accuracy in clinical use (in Japanese)



Satoshi Nakamura, et al.
Department of Medical Physics, National Cancer Center Hospital

An accelerator-based boron neutron capture therapy (BNCT) system with a Li target (Cancer Intelligence Care Systems) has been installed at the National Cancer Center Hospital. Previous studies have reported that the neutron output per unit number of protons of the accelerator-based BNCT system decreases dependent on the integrated proton dose to the Li target[1,2] . To use this system clinically, a default neutron fluence must be delivered to the patient, and it is necessary to estimate the reduction in neutron power that occurs during treatment before the patient is treated. Therefore, a theoretical model for the neutron power reduction per unit proton fluence was developed, and its accuracy and validity were verified based on measured data. Furthermore, assuming the clinical use of the accelerator-based BNCT system, we predicted the neutron output after the irradiation of the assumed quantity of protons required for the BNCT treatment using the theoretical model and evaluated the accuracy of the model.

The acceptable output of radiotherapy equipment is within ±2% as recommended in the QA system guideline for external radiation therapy by the Japanese Society of Radiation Oncology, and the same accuracy should be achieved for the accelerator BCNT system and neutron output.

The theoretical model constructed from the present results adequately reproduces the measured values and has been validated.[3] The results also satisfied the acceptable output values recommended in the QA system guidelines for external radiotherapy when the system was assumed to be used clinically.

The data were obtained from a portion of a non-clinical study of the accelerator-based BNCT system installed at the hospital. Based on those data, our hospital is conducting

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phase I clinical trials for malignant melanoma and angiosarcoma from 2019. We will continue to exert every effort to conduct research that will lead to the development of neutron capture therapy.

Finally, I would like to express my sincerest gratitude to all who were involved in this opportunity.

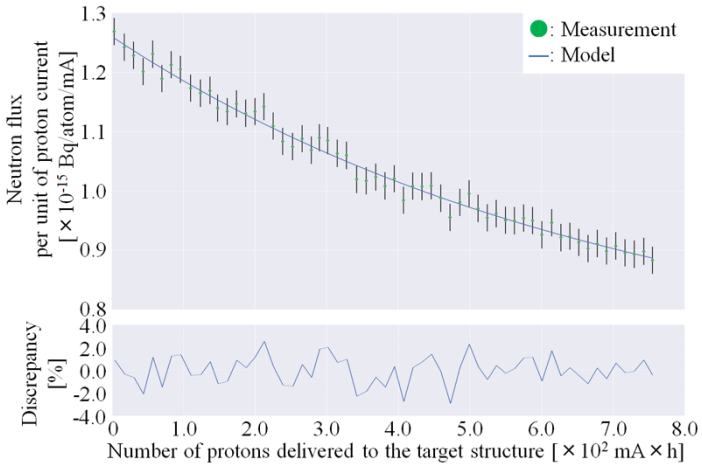

Fig. 1: The effect of proton irradiation on the Li target as a function of the integrated proton fluence. Comparison of measured neutron output and calculated values by the model (Measured value: evaluated by the saturated radioactivity of gold).

1) Nakamura S et al., Dependence of neutrons generated by ^{7}Li(p,n) reaction on Li thickness under free-air condition in accelerator-based boron neutron capture therapy system. Phys. Med. 58: 121-130 (2019)
2) Nakamura S, et al., Characterization of the relationship between neutron production and thermal load on a target material in an accelerator-based boron neutron capture therapy system employing a solid-state Li target. PLoS One. 14(11): e0225587 (2019)
3) Nakamura S, et al., Neutron flux evaluation model provided in the accelerator-based boron neutron capture therapy system employing a solid-state lithium target. Sci. Rep. 11(1): 8090 (2021)

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

Optimization of dose calculation algorithm for BNCT by a combination of Monte Carlo and superposition methods

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Recently, boron neutron capture therapy (BNCT) clinical treatment using an accelerator-based neutron source has been provided for some cancers. Although the Monte Carlo (MC) method has been conventionally used as a dose calculation algorithm for BNCT because of its high accuracy, it takes a few hours to obtain distribution with high accuracy. Therefore, we are developing a hybrid algorithm combining the superposition method and the MC method to accelerate the dose calculation. In this algorithm, the neutron moderation process is calculated by the MC method and the thermalization process is modeled as a kernel. For shortening the calculation time, the thermalization process, which is time-consuming to calculate, is prepared as a kernel in advance, and the transport calculation by the MC method is terminated when neutron energy reaches the lower limit (cutoff energy) to shift from the moderation process to the thermalization process. In this study, the calculation accuracy of the algorithm is experimentally verified, and the cutoff energy is optimized.

First, the content of the calculation using the hybrid algorithm is described as follows. For the calculation of the kernel, a sufficiently large geometry filled with boric acid water was used. The distribution of thermal neutron fluxes generated from a point source with the same energy as the cutoff energy was derived in the geometry and used as the kernel. Then, the flux distribution of neutrons that stop at the cutoff energy was obtained by terminating the transport calculation by the MC method using the cut-off function in the geometry that simulated the experiment as described below. The final thermal neutron flux distribution was then derived by convolution-integration of the distribution with the kernel.

Next, we describe a method for measuring thermal neutron flux using the gold activation method. After a gold wire was placed on the central axis of a cubic phantom filled with boric acid water, the phantom was irradiated by the epi-thermal neutron beam in the heavy water neutron irradiation facility of the Kyoto University Research Reactor. Thereafter, the radioactivity of the activated gold wire at each position was measured by a gamma-ray detector, and the thermal neutron flux was obtained from the reaction rate of the gold wire.

Finally, we discuss the optimization of the cutoff energy. In this study, the cutoff energies in the hybrid algorithm were set to 1, 2, 3, 4, 5, and 10 eV. The accuracy and time were evaluated for each cutoff energy by comparing the thermal neutron distribution obtained by the experiment with the calculations described above and by comparing the calculation results with those by the full-energy MC method.

First, when the cutoff energy was set to 1 eV, the thermal neutron flux distribution calculated by the hybrid algorithm was in good agreement with the experimental data at

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depths greater than 4 cm from the phantom surface. However, it overestimated the experimental data in the shallower region, and the kernel should be improved. The values calculated by the full-energy MC method were in good agreement with the experimental values. In addition, when the cutoff energy was set to 2 eV, the same trend with the reproduction shown when the cutoff energy was set to 1 eV. However, when the cutoff energy was set to 3 eV or more, the difference from the values calculated by the full-energy MC method became bigger. Furthermore, as the cutoff energy was increased, the calculation time per the same number of particles became shorter, however, the difference became smaller. The convergence of the statistical uncertainty was faster when the cutoff energy was set to 1 or 2 eV. These results suggested that 1 or 2 eV was the optimal cutoff energy.

In this study, the calculation accuracy of the hybrid algorithm was experimentally verified. In addition, the accuracy and time of the hybrid algorithm were evaluated, while the cutoff energy was changed, to optimize the cutoff energy. As a result, we confirmed that the calculation using the hybrid algorithm partially reproduces the experimental results well, and the optimal cutoff energy was considered to be 1 or 2 eV. In the future, we will develop the algorithm including the improvement of the kernel to realize more accurate and faster dose calculation.

Finally, I would like to express my sincere appreciation to Dr. Jun Itami, the President of the Congress; Dr. Minoru Suzuki, the President of the Society; all the members of the Management Office of the 17th Annual Meeting of the Neutron Capture Therapy Society; and the judges for selecting this presentation for the Best Presentation Award, as well as to the following people for their kind cooperation in the NCT letter. I would like to thank Dr. Mitsuko Masutani for giving me the opportunity to write this article. I would also like to thank Dr. Hiroki Tanaka, Dr. Yoshinori Sakurai, Dr. Takushi Takata, and Dr. Naonori Hu for their help in presenting this study.

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

NCT letter (English version) Vol. 8 September, 2022
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Therapeutic effect of boron neutron capture therapy using a novel boron compound targeting 18 kDa translocator protein (TSPO) on F98 rat model of malignant glioma

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Osaka Medical and Pharmaceutical University

Background: Malignant gliomas are intractable diseases that easily recur from residual tumors even after complete surgical treatment and postoperative radiation chemotherapy because of their invasive growth into the normal brain. Therefore, postoperative therapy must be highly biologically targeted, as it must be able to select tumor cells that have invaded the normal brain. The efficacy of BNCT in the treatment of malignant gliomas has been demonstrated, but complete cure has not yet been achieved, and the development of new boron compounds with different biological targeting properties from BPA is desired. Recently, it has been demonstrated that TSPO-targeted tracer is highly concentrated in malignant gliomas in positron emission tomography (PET) scans targeting 18-kDa TSPO, and that recurrence of malignant gliomas is detected earlier than in contrast-enhanced MRI scans. We have been conducting basic research on TSPO-targeted BNCT using the F98 rat glioma model and reported the results obtained thus far.

Methods: In vitro, we confirmed TSPO expression in F98, 9L, and C6 rat glioma cells. BPA, BSH, and TSPO-targeted boron compounds were used to evaluate boron accumulation in tumor cells in several malignant tumor cell lines. In F98 rat glioma cells, after each boron compound exposure, neutron irradiation and the estimated biological effect coefficients were calculated.
In vivo, TSPO expression in tumors of the F98 rat brain tumor model was evaluated. In the biodistribution evaluation, the intravenous administration (IV) of the TSPO target boron compound did not give a sufficient intratumoral boron concentration. Therefore, we chose convection-enhanced delivery (CED) administration, which is a local dosing method. BPA was evaluated using IV.
In neutron irradiation experiments using the F98 rat glioma model, the following groups were used: untreated control group, neutron irradiated control group, TSPO-targeted boron compound (CED) control group, BPA (IV) BNCT group, TSPO-targeted boron

compound (CED) BNCT group, TSPO-targeted boron compound (CED)-BPA (IV) BNCT group, TSPO-targeted boron compound (CED) BNCT group, and TSPO-targeted boron compound (CED)/BPA (IV) BNCT group, and the treatment efficacy was evaluated by survival.

Result: Three rat glioma cells were found to express TSPO; in F98 rat glioma cells, boron accumulation in TSPO-targeted boron compound exposure was higher than that in BPA or BSH exposure, and the estimated biological effect coefficient after neutron irradiation was the highest among boron compounds.
In the F98 rat glioma model, TSPO was highly expressed in tumors 16-fold in contralateral normal brain tissue. Biodistribution evaluation showed that the TSPO-targeted boron compound (CED) group yielded more than twice the intratumor boron concentration of the BPA (IV) group.
In neutron irradiation experiments using the F98 rat brain tumor model, both BNCT-treated groups showed a significant survival advantage over untreated controls; the TSPO-targeted boron compound (CED) BNCT group showed no significant survival advantage over the BPA (IV) BNCT group; however, the BPA (IV) and TSPO-targeted boron compound (CED) BNCT group obtained a significant prolongation of survival compared to the BPA (IV) BNCT group.

Conclusion: TSPO-targeted PET for malignant gliomas has already developed several TSPO-targeted tracers to estimate patients suitable for BNCT; malignant gliomas with high expression of TSPO may be expected to take up TSPO-targeted boron compounds, and TSPO-targeted boron compounds (CEDs) and BPA (IV) in combination with BPA (IV) are promising agents for BNCT for malignant gliomas, adding a cell-killing effect to cells that are inadequately treated by BNCT with BPA alone.

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

NCT letter (English version) Vol. 8 September, 2022
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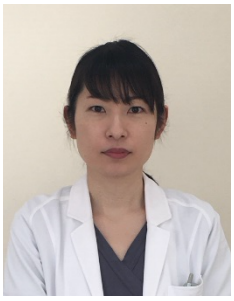
Initial treatment experience of BNCT after insurance coverage



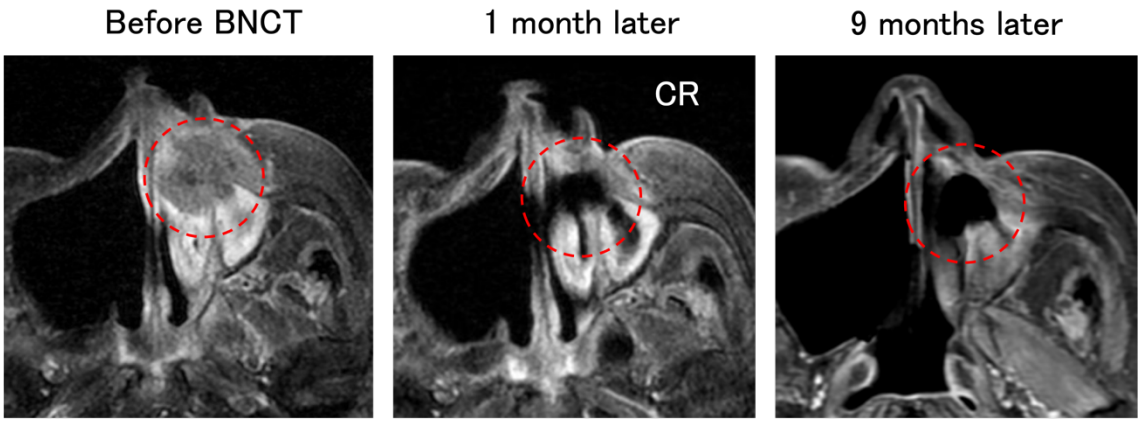
Mariko Sato, et al.
Department of Radiation Oncology,
Southern Tohoku BNCT Research Center

Insurance reimbursement for BNCT for unresectable advanced or locally recurrent head and neck cancer began in June 2020. We have performed 78 cases of BNCT in our hospital in the following 1 year, and we present three cases as our initial experience.

All patients were treated using the clinical pathway and were hospitalized for 1 week after irradiation to deal with acute adverse events. All treatments were performed with sitting immobilization and a maximum mucosal dose of 12 Gy-Eq prescription.

[Case 1] A female in her 80s, with left maxillary gingival cancer recurrence, SCC, rT4aN0M0

The patient was referred to our department because of recurrence of right maxillary gingival carcinoma after 70 Gy combined dynamic radiotherapy and postoperative left maxillary gingival carcinoma after 24 Gy combined dynamic radiotherapy. Four hours after irradiation, oral pain was noted and analgesics were started; however, the patient was discharged on day 7 in good general condition. After discharge, oral mucositis (Gr. 3), epistaxis (Gr. 1), and alopecia appeared. The left maxillary tumor decreased in size on day 3, and MRI 1 month after irradiation showed that the mass had disappeared, and the patient was considered to be CR. CR was maintained at the visit 9 months after irradiation (Figure below).



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[Case 2] A female in her 50s, recurrent cancer of the right external auditory canal, SCC, rT0N3bM0

The patient was referred to our department after chemoradiotherapy (80 Gy) and postoperative recurrence, and MRI showed a soft shadow with contrast effect in the right interpharyngeal space and PET showed FDG accumulation with SUVmax 11.0. BNCT was performed and GTV dose was 41.7 max, 26.8 min, and 33.6 Gy-Eq on average. Right neck pain (Gr. 2) was noted 5 h after irradiation, including nausea (Gr. 3) and decreased appetite (Gr. 3) from day 1, which were treated symptomatically. Her symptoms gradually improved and she was discharged on day 7. After discharge, oral mucositis (Gr. 2), decreased taste (Gr. 1), and alopecia appeared. Three months after irradiation, SUVmax decreased to 2.8 on PET, and soft-tissue shadows disappeared on MRI; hence, the patient was considered CR. However, a PET scan 6 months after irradiation showed reappearance of FDG accumulation with an SUVmax of 6.9 at the same site, and a diagnosis of recurrence was made.

[Case 3] A male in his 70s, recurrent tongue cancer, SCC, rT1N2aM0

The patient was referred to our department because of local recurrence of the tongue and left cervical lymph node after radiotherapy (70 Gy). The GTV dose was max 40.1, min 20.8, mean 29.8 Gy-Eq. Nausea (Gr. 2) from day 1 and fatigue (Gr. 1) and decreased appetite (Gr. 2) from day 2 were observed. On day 6, he developed fever and CT showed aspiration pneumonia; thus, antibiotics were initiated. On MRI at 3 months, the metastatic lymph node had shrunk and was considered to be CR; 6 months later, the patient was still in CR.

All of the above cases were recurrent cases, but responded well to BNCT. While some patients showed rapid tumor shrinkage and maintained CR in a short period of time after irradiation, others developed recurrence after CR, requiring careful follow-up. In the acute phase, adverse events such as pain, nausea, decreased appetite, and mucositis were observed, and attention should also be paid to aspiration pneumonia, especially in elderly patients. However, most patients can be discharged from the hospital within 1 week after irradiation with symptomatic treatment.

The Best Presentation Award of the 17th annual Congress on Japanese Society of Neutron Capture Therapy

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Footprint and future prospects of human resource development activities by the Human Resources Development Committee of the Japan Society for Neutron Capture Therapy

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Osaka Prefecture University

Thank you very much for selecting us for the Best Presentation Award at the 17th Annual Meeting of the Japanese Society for Neutron Capture Therapy. We have updated the contents of the abstracts presented at the conference.

The aim of this project is to provide human resources in medical physics for the comprehensive development of basic research, clinical research, and medical advancement of BNCT, targeting all creative researchers who are interested in participating in BNCT as staff, not only those with physics and engineering backgrounds but also those with medical and pharmaceutical backgrounds. The BNCT version of the Medical Physicists WG was established, consisting of committee members. The WG has the following objectives: (1) organize seminars at the time of the annual meeting for specialized and interested researchers, (2) conduct social awareness-raising activities on BNCT, (3) discuss the special nature of BNCT work and the ideal educational organization, (4) discuss the knowledge that NCT medical physicists (tentative name) and NCT medical physicists (tentative name) should acquire and develop their applied skills for optimizing NCT, and (5) discuss the role of NCT as a medical physics professional and discuss the role of NCT as a medical science profession. The activities of the committee included the development of guidelines. In particular, with regard to human resource development, it was decided to develop appropriate human resources by establishing an educational organization related to NCT, to realize the sound development of NCT and contribute to the health and welfare of the public, and to establish the status of staff involved in the NCT (especially medical physics-related staff) who are not stipulated by laws and regulations.

Thereafter, at the 9th-JSNCT (Japanese Society for Neutron Capture Therapy) and 15th-ICNCT (International Conference on Neutron Capture Therapy) Society Executive Committee Meeting (Tsukuba) in September 2012, it was decided that a workshop was held at the next JSNCT Annual Conference and that a joint committee for "BNCT Human Resource Development Study Group (tentative name)" with the Atomic Energy

Society of Japan was organized. A proposal was made and approved to work towards the establishment of a new committee.

Based on this approval, the following events were held: the1st BNCT Medical Physics Workshop (September 8, 2013, two lectures [both physics], pre-registration of 47 people, on-site registration of three people, 10th-JSNCT-Okayama); the 2nd BNCT Medical Physics Workshop (July 4, 2014, three lectures (biology, nuclear medicine, pharmacy), pre-registration of 79 people, on-site registration of 32 people, 11th-JSNCT-Osaka); and the 3rd BNCT Medical Physics Workshop (September 3, 2015, three lectures (pharmacy, clinical, physics), pre-registration of 67 people, on-site registration of 23 people, 12th- JSNCT-Kobe).

The BNCT version of the Medical Physicists WG has been performing practical work related to human resource development for BNCT, such as holding workshops at academic conferences and sponsoring the BNCT workshop organized by the BNCT Research Group at the Kyoto University Research Reactor Institute. The usefulness of these activities was evaluated, and this WG was re-established as the "BNCT Human Resource Development Committee" (chaired by S. Masunaga) with nine new members and 15 members in total at the annual meeting of the Japanese Society for Neutron Capture Therapy in 2015. The main tasks of this committee are to train BNCT specialists (BNCT physicians and BNCT physicists or engineers) to ensure the future development of BNCT and to promote social awareness of BNCT as one of established medical treatment modalities.

Thereafter, the following events were held by the "BNCT Human Resources Development Committee": the 4th BNCT Workshop (August 5, 2016, three lectures (clinical, biology, pharmacy), pre-registration of 48 people, on-site registration of 24 people, 13th- JSNCT-Tokyo), the 5th BNCT Workshop (September 28, 2017, visited South Tohoku BNCT Research Center, two lectures (About South Tohoku BNCT Research Center, Accelerator BNCT), registration for participation of 89 people, 14th-JSNCT-Koriyama, Fukushima), the 6th BNCT Workshop (August 31, 2018, two lectures (both physics), pre-registration of 23 people, on-site registration of eight people, 15th- JSNCT-Sapporo, Hokkaido), the 7th BNCT Workshop (September 8, 2019, two lectures (physics, clinical), pre-registration of 16 people, on-site registration of 10 people, 16th- JSNCT-Uji, Kyoto), the 8th BNCT Workshop (December 23-24, 2020, held online by Zoom, co-sponsored by the BNCT Promotion Council Human Resources Development WG, with 36 participants, Kumatori, Osaka), and the 9th BNCT Workshop (July 11, 2021, held online, 17th-JSNCT-Atami, symposium in the academic conference in Shizuoka, with 78 participants).

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In order for Japan to lead the world in NCT, JSNCT will take the lead in the near future; however, from the viewpoint of human resource development, it is necessary for each research institute and medical center to conduct lectures and practical training under the leadership of each facility that has its own neutron source. It is considered essential. Furthermore, in the future, it would be desirable to implement human resource development that organically links specialized NCT basic education and NCT clinical practice education, and to have an organization named "NCT Human Resource Development Center" that coordinates the promotion of NCT and comprehensively takes charge of tasks such as coordination among these centers and organization of training course.

Finally, I would like to thank the members of the Human Resource Development Committee of the Japanese Society for Neutron Capture Therapy for their great support and cooperation in conducting the activities of the committee, especially Dr. Takada Takushi and Dr. Maruhashi Akira, who were members of the committee and co-authors of the paper, and Dr. K. Kato, who was a member of the committee. We would like to express our deep appreciation to Dr. Hiroyuki Nakamura, the former President of the Japanese Society for Neutron Capture Therapy, and Dr. Minoru Suzuki, the present President of the society. We also thank Dr. Jun Itami, the President of the 17th Annual Meeting of the Japanese Society for Neutron Capture Therapy, who selected our presentation for the Best Presentation Award, and all the other related authors who took their time to review the presentation. I would like to express my sincere gratitude to Dr. Mitsuko Masutani, who is Chairman of the NCT letter editorial committee, for giving me the opportunity to write this article.

● *Introduction of the articles*

<Pharmaceutical Science >

Presented by *Makoto Shirakawa*

Department of Pharmaceutical Sciences, Fukuyama University

Title: Addressing the Biochemical Foundations of a Glucose-Based “Trojan Horse”-Strategy to Boron Neutron Capture Therapy: From Chemical Synthesis to In Vitro Assessment

Authors：Jelena Matović, Juulia Järvinen, Helena C. Bland, Iris K. Sokka, Surachet Imlimthan, Ruth Mateu Ferrando, Kristiina M. Huttunen, Juri Timonen, Sirpa

Peräniemi, Olli Aitio, Anu J. Airaksinen, Mirkka Sarparanta, Mikael P. Johansson, Jarkko Rautio, and Filip S. Ekholm
The source: Molecular Pharmaceutics, 17, 3885−3899 (2020)
https://doi.org/10.1021/acs.molpharmaceut.0c00630

Comments:
In 2020, NeuCure™, a medical device for BNCT and the boron drug Steboronin® received marketing authorization for head and neck cancer and will enter the phase of indication expansion. In BNCT, intracellular boron delivery via LAT-1, represented by BPA, is often the focus, but tumor LAT-1 is not always highly expressed in some cells. The CAL27 cell line used in this study has minimal BPA uptake (or sequestration), and strategies other than LAT-1 are required to achieve a therapeutic effect with BNCT. Some other carcinomas are known to be hepatoma (FLC-4 cell line) and breast cancer (MDA-MB-231-luc cell line) (T. Andoh, et. al, *Appl. Radiat. Isot*., 2020 Nov;165:109257., P. Wongthai., et. al, *Cancer Sci*. 2015 Mar; 106(3): 279-286.) As we aim to expand the indications for BNCT in the future, boron delivery studies using transporters other than LAT-1 are of great significance, and this report targeting GLUT1 is expected to contribute to the advancement of BNCT. Jelena Matovic et al. also reported a comparison of o-carbaborane binding sites *in* Glucoconjugate (*Mol. Pharmaceutics*, 2021, 18, 285-304). We will wait for further *in vivo studies* such as the therapeutic effects of neutron irradiation in animal models of carcinoma.
With your permission, my research group also reported glucoconjugate of sugar (D-glucose, D-galactose) and BSH at the annual meeting of the Glycoscience Society of Japan in 2018. We have delayed the *in vitro* and *in vivo* evaluations due to our hectic schedule, but we are planning to reexamine the usefulness of the in *vitro* and *in vivo* evaluations with reference to these reports.

<Physical Engineering >

Presented by *Kenichi Tanaka*
Division of Advanced Science and Engineering,
Hiroshima University

Title : ^{124}Sb-Be photon-neutron source for BNCT: Is it possible?
Authors : Mohadeseh Golshanian, Ali Rajabi, Yaser Kasesaz

ISSN 2758-285X

The source: Nuclear Instruments and Methods in Physics Research A836 (2016) 182-185

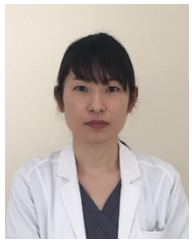
Comments:

The paper was about BNCT in a moderator-free beam forming section using ^{124}Sb-Be, which can selectively produce neutrons in the 21-24 keV range, which is close to the extra-thermal region, or is treated as the extra-thermal region in some facilities. I had also considered the same point of view (Appl. Rad. Isot. 164 (2020)109227) before and after the paper, but the γ rays from ^{124}Sb require tens of cm of shielding for adequate quality. Therefore, although the beam forming part within 1 m is good, 10^{16} Bq order and ^{124}Sb with large radioactivity are required. Because its half-life is about 60 days, procuring ^{124}Sb will be a practical issue.

Neutron sources using isotopes have the advantage of being stable in time and are small in size and have a high degree of freedom in operation. In terms of licensing, it also has the advantage of an accelerator that it is easy to install in a hospital near the city. In addition, the only thing that needs to be controlled is the positional relationship between the source and the target, which has the advantage of a simple and trouble-free structure. It is meaningful for the BNCT industry to sort out the conditions for using isotopes-nuclear reactions as the third neutron source. This paper showed an approach to reduce the neutron loss by suppression of the generated neutron energy and reduction of moderator size.

<Medicine>

Presented by *Mariko Sato*
Department of Radiation Oncology,
Southern Tohoku BNCT Research Center



Title: Accelerator-based BNCT for patients with recurrent glioblastoma: a multicenter phase II study

Authors： Shinji Kawabata, Minoru Suzuki, Katsumi Hirose, Hiroki Tanaka, Takahiro Kato, Hiromi Goto, Yoshitaka Narita, Shin-Ichi Miyatake

The source: Neuro-Oncology Advances, Volume 3, Issue 1, January-December 2021, vdab067, https://doi.org/10.1093/noajnl/vdab067

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Comments:.

Malignant gliomas, especially glioblastomas, have very poor prognosis and are characterized by high invasiveness and rapid proliferation. BNCT is expected to be a new treatment option for glioblastoma because of its cell-selective nature and single high-dose irradiation.

The 1-year overall survival (OS) and median OS shown in this study were both significantly higher than the results of the JO22506 trial. Conversely, the 6-month progression-free survival (PFS) of 5.3% and mPFS of 0.9 months compare unfavorably with the 33.9% and 3.3 months in JO22506, indicating a reversal. This can be expected because many pseudo progressions after re-irradiation by BNCT were included in the PD evaluation, and the limitation of the RANO criteria for efficacy evaluation is considered to be truly apparent.

Radiation brain necrosis occurs frequently after radiation therapy with TMZ, which is the standard of care for malignant gliomas, with a reported frequency of 30% or more (Alba A. Brandes et al. J Clin Oncol. 26:2192-2197, 2008). The RANO criteria (Wen PY et al. J Clin Oncol. 28:1963-1972, 2010) are based on post-treatment outcomes. It was developed to distinguish between pseudo-progression and recurrence, with PD defined as the appearance of a new contrast-enhanced lesion outside the high-dose or 80% isodose range within 12 weeks after chemoradiotherapy. However, the RANO criteria may not be appropriate for determining the efficacy of re-irradiation, and in the future, at least a superimposition of the BNCT dose distribution chart and the dose distribution chart of the previous treatment should be performed to determine the efficacy of re-irradiation. The accumulation of data on the evaluation using cumulative doses after matching the data will be necessary.

It is also noteworthy that KPS was preserved after BNCT, which may indicate the benefit of cell-selective BNCT. Although the majority of patients in this study had KPS > 80% at enrollment, only two of the 13 patients with evaluable KPS at 12 months after BNCT had KPS < 50% (original article, Figure 3). The ability to maintain ADLs for a relatively long period of time, even though many patients are receiving BEV due to PD, represents a very significant treatment option for malignant gliomas.

This study shows that BNCT can be performed safely and effectively, especially in patients with KPS > 80%, first recurrence, and relatively small tumor volume. It will be important to establish a medical system that allows careful imaging follow-up after standard treatment and prompt selection of BNCT when recurrence is diagnosed. With very limited treatment options available, insurance reimbursement for BNCT for malignant gliomas is anticipated.

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<Biology>

Presented by *Natsuko Kondo*
Institute for Integrated Radiation and Nuclear Science, Kyoto University

Title: Evaluation of local, regional and abscopal effects of Boron Neutron Capture Therapy (BNCT) combined with immunotherapy in an ectopic colon cancer model

Authors：Trivillin VA, Langle YV, Palmieri MA, Pozzi ECC, Thorp SI, Benitez Frydryk DN, Garabalino MA, Monti Hughes A, Curotto PM, Colombo LL, Santa Cruz IS, Ramos PS, Itoiz ME, Argüelles C, Eiján AM, Schwint AE.
The source: Br J Radiol 2021; 94: 20210593.

Comments:
It has been reported that an abscopal effect occurs when immune checkpoint inhibitors are combined with X-ray therapy, and we have heard that various clinical studies are being conducted. BCG is known as a local immunomodulator, but local and abscopal effects have been reported when BCG is combined with low LET radiation. The direct effect of DNA damage is stronger. The abscopal effect is thought to be caused by the activation of immune signaling by damaged double-stranded DNA. In this paper, a colon cancer transplantation model was used, but translational studies that can be applied to clinical practice, such as those with other cancer types or in combination with BPA-BNCT with other immunotherapeutic drugs, are increasingly needed.

● *Editorial Postscript*

Mitsuko Masutani
Chief Editor of NCT letter
Professor, Graduate School of Biomedical Sciences, Nagasaki University

I would like to take this opportunity to congratulate all the members of the Japanese Society for Neutron Capture Therapy (JSCT). Under the guidance of the former editor-in-chief, Dr. Itsuro Kato (Osaka University), Dr. Teruki Kageji (Tokushima Prefectural Kaifu Hospital), and Dr. Minoru Suzuki (Kyoto University), and with the cooperation of all the authors, the newly joined editorial board members, Dr. Toru Ando (Kobe Gakuin University), Dr. Isao Murata (Osaka University), Dr. Kazuhiro Nakamura (Osaka University), and Dr. Kazuhiro Kato (Osaka University), have been working hard to improve the quality of our work. We also thank Dr. Kazuyo Igawa (Okayama University), Dr. Katsumi Hirose (Minami-Tohoku BNCT Center), Dr. Tsubasa Watanabe (Kyoto University), Dr. Shoji Imamichi (Nagasaki University), Dr. Shinji Kawabata (Osaka Medical and Pharmaceutical University), Dr. Hiroki Tanaka (Kyoto University), Dr. Koki Matsumoto (University of Tsukuba), Dr. Takahiro Nomoto (Tokyo Institute of Technology), Dr. Tetsushi Nakamura (National Cancer Center), Dr. Tetsushi Nakamura (National Cancer Center), and Dr. Tetsuo Kurokawa (Osaka University). We would like to thank Dr. Hiroshi Igaki (National Cancer Center) and Dr. Teruhito Aihara (Osaka Medical and Pharmaceutical University) for their efforts in publishing NCT letter No. 8.

The preface of this issue, "Prologue to the NCT letter No.8", is written by Dr. Minoru Suzuki, President of NCT, which is about the participation of the Institute for Integrated Radiation and Nuclear Science, Kyoto University in the joint research.

In the special feature article, Dr. Hiroki Tanaka of the Research Institute for Composite Nuclear Science, Kyoto University, gave an overview of medical physics research in BNCT; Dr. Tomoyuki Asano of Stella Pharma Corporation. talked about the BPA preparation Steboronin®, which was approved in 2020, and Dr. Kazuhiro Nakagawa of the University of Tokyo talked about the companionship of Dr. Minoru Suzuki who has written an article on the BNCT indication expansion research for animals.

The 17th Annual Meeting of the Japanese Society for Neutron Capture Therapy (JSNCT), which was postponed for 1 year due to the coronavirus pandemic, was held with the efforts of all concerned, and Dr. Jun Itami, the chairman of the organizing committee, wrote a report on the meeting.

Dr. Koji Ono, the winner of the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, and the 10 winners of the Best Presentation Award at the 17th Annual Meeting of the Japanese Society for Neutron Capture Therapy have contributed to this issue. In the paper introduction, Dr.

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Makoto Shirakawa, Dr. Kenichi Tanaka, Dr. Mariko Sato, and Dr. Natsuko Kondo explained recent noteworthy papers in an easy-to-understand manner.

The bulletin board contains information about the operation and activities of the Japanese Society for Neutron Capture Therapy (JSNCT), as well as updates to the website.

The NCT letter editorial committee looks forward to the future activities of all the members of the society and has started to prepare the next issue of the NCT letter, hoping to transmit your activities in real time as much as possible. We would like to feature a wide range of articles on BNCT, including new projects and desired submissions to the journal. We would be very grateful if you could send your frank opinions and information to the NCT letter editorial committee members.

Thank you very much for your cooperation.