NCT letter Vol. 5

（English version）

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[1]Southern Tohoku BNCT Research Center

● *Introduction of the articles*

1. **<Physics >**

Title: Development of An Epi-thermal Neutron Field for Fundamental Researches for BNCT with A DT Neutron Source

Authors: Yuta Osawa, Shoichi Imoto, Sachie Kusaka, Fuminobu Sato, Masahiro Tanoshita and Isao Murata

The source: EPJ Web of Conferences 153, 04008, 2017

https://doi.org/10.1051/epjconf/201715304008

Presented by *Shingo Tamaki* (Graduate School of Engineering, Osaka University)

2. **<Physics >**

Title: BGO as a hybrid scintillator/Cherenkov radiator for cost effective time-of-flight PET

Authors: S.E. Brunner and D.R. Schaart

The source: Physics in Medicine & Biology (2017) 62: 4421-4439

https://doi.org/10.1088/1361-6560/aa6a49

Presented by *Tatsushi Shima* and *Ryoichi Seki* (Research Center for Nuclear Physics Osaka University)

3. **<Pharmacology>**

Title: Comparison of the pharmacokinetics between L-BPA and L-FBPA using the same administration dose and protocol: a validation study for the theranostic approach using [^{18}F]-L-FBPA positron emission tomography in boron neutron capture therapy

Authors: Tsubasa Watanabe, Yoshihide Hattori, Youichiro Ohta, Miki Ishimura, Yosuke Nakagawa, Yu Sanada, Hiroki Tanaka, Satoshi Fukutani, Shin-ichiro Masunaga, Masahiro Hiraoka, Koji Ono, Minoru Suzuki and Mitsunori Kirihata

The source: BMC Cancer (2016) 16:859

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5100278/

Presented by *Yoshihide Hattori* (BNCT Research Center, Osaka prefecture University)

4. **<Biology>**

Title: Abscopal effect of boron neutron capture therapy (BNCT): proof of principle in an experimental model of colon cancer

Authors: Verónica A. Trivillin, Emiliano C. C. Pozzi, Lucas L. Colombo, Silvia I. Thorp, Marcela A. Garabalino, Andrea Monti Hughes, Sara J. González, Rubén O.

Farías, Paula Curotto, Gustavo A. Santa Cruz, Daniel G. Carando, Amanda E. Schwint

The sources: Radiation and Environmental Biophysics (2017) 56(4):365-375

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5100278/

Presented by *Yu Sanada* (Particle Radiation Biology, Division of Radiation Life Science, Kyoto University Institute for Integrated Radiation and Nuclear Science)

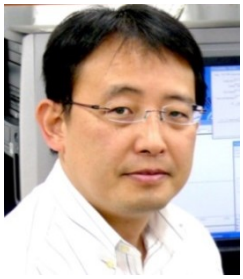
● *Editorial Postscript*

Itsuro Kato

Chief Editor of NCT letter

Department of Oral and Maxillofacial Surgery II, Graduate School of Dentistry, Osaka University

On the occasion of the publication of NCT letter issue No.5



Hiroyuki Nakamura
President
Japanese Society of Neutron Capture Therapy
(Professor of the Institute of Innovative Research, Tokyo Institute of Technology)

Thanks to the efforts of Dr. Itsuro Kato, who has taken up the post of chairperson of NCT letter editorial committee this year, and through cooperation with our colleagues, the fifth issue of NCT letter was published. I take this opportunity to express my sincere gratitude.

Currently clinical trials using the world's first accelerator-based neutron sources for brain tumors and for head and neck cancer are underway. This therapy will soon be put into practical use. Also, the boron neutron capture therapy (BNCT) system (February 2017) and boron agents "SPM-011" for BNCT (April 2017) are designated by the Ministry of Health, Labour, and Welfare (MHLW) for "prioritized review system for innovative medicines" to enable a rapid review for approval under the Pharmaceuticals and Medical Devices Law, accelerating the process. After these designations, "development of guidance for the approval process of brand-new medical products and regenerative medicine products" and "development of guidelines for further development and practical use of medical devices" for BNCT have been underway since last year in collaboration with MHLW and the Ministry of Economy, Trade and Industry (METI). As a feature article illustrates, A 2017 WG report for BNCT review was compiled under the leadership of Dr. Junichi Hiratsuka, professor of Kawasaki Medical University and is now on the National Institute of Health Sciences website*. Our fellow members are invited to see the report. Also in JSNCT, a reorganized working group has been developing, since September 2017, a treatment guidebook for accelerator-based BPA-BNCT under the leadership of Dr. Minoru Suzuki, professor of Institute for Integrated Radiation and Nuclear Science, Kyoto University, in cooperation with Japanese Society for Radiation Oncology and Japanese Society of Nuclear Medicine.

As a feature article illustrates, in January 2018, BNCT Medical Center was established, attached to Osaka Medical College, under its first director Dr. Koji Ono, professor emeritus of Kyoto University. As seen above, medical bases for BNCT are

steadily being developed, showing a clearer path for “treatment within the reach of patients” along with the progress of clinical trials.

Based on these situations, JSNCT implements BNCT safely, and addresses, in addition to the existing BNCT human resource development program, a well-planned training of certified medical practitioners with appropriate expertise by developing “new JSNCT qualification criteria for certified medical practitioners” and by introducing the qualification test since last year, in the aim of further expanded use of the therapy. With the progression of phase II accelerator-based BNCT clinical trials for brain tumor and for head and neck cancer, we are now approaching a critical stage toward the review for early approval of BNCT. We ask for your understanding and cooperation in order that our fellow members unite to realize “treatment within the reach of patients” under an all-Japan cooperative approach.

*URL:http://dmd.nihs.go.jp/jisedai/bnct_for_public/

As director of Kansai BNCT Medical Center, Osaka Medical College

Koji Ono
Director
Kansai BNCT Medical Center, Osaka Medical College

On January 1st, 2018, I was appointed to director of Kansai BNCT Medical Center, Osaka Medical College. I would like to take this occasion to convey my greetings to our fellow members of the Japanese Society of Neutron Capture Therapy

As you all know well, a basic idea of BNCT was proposed by an American physician in 1936, four years after the discovery of neutron. In the 1950s, after World War II, when nuclear reactors began to be used not only for manufacturing and research of nuclear weapons but also for research of peaceful purposes, clinical studies started in the US. But honestly speaking, these studies ended up in failure, because they had problems with boron agents and neutron beam. It was Japanese researchers including the late Dr. Hatanaka and the late Dr. Mishima who have changed the situation. Though the results of Dr. Hatanaka's clinical study on brain tumor with BSH was attractive, experts on radiology and neurosurgery didn't appreciate these achievements, as they lacked sufficient scientific information due to limitations associated with the developmental stage of the study. Thinking back now, it was insufficient in basic research as well. Today's development in BNCT was not triggered by BSH but by the arrival of BPA. It is clear that, without research on BPA-based BNCT led by Dr. Mishima, actual BNCT wouldn't exist. They organized a comprehensive group of researchers in the fields of nuclear engineering, boron chemistry, radiobiology, radiation oncology, nuclear medicine and medical physics, as well as clinical dermatology. The first clinical treatment using BPA of a patient with melanoma was carried out in 1987, when I first got involved in BNCT. Then fate led me to become a professor of Kyoto University Research Reactor Institute in 1991, where I carried responsibility for research on BNCT. Fortunately, I have successfully brought together many researchers who would pursue their research on BNCT using Kyoto University Research Reactor, especially from the Kansai region. Joint studies are primarily led by researchers in radiation oncology, of course, neurosurgery, head and neck oncology, dermatology and nuclear medicine. With them, we have carried out many world first clinical trials which lead research on BNCT. In the Kansai region, following this active research, researchers

have commonly recognized the need to establish a hub in order to link achievements in basic research in research centers including Kyoto University (Research Reactor Institute), Osaka University and Osaka Prefecture University to clinical therapy. Responding to that demand, we decided to establish a clinical hub within our university. Under such circumstances, our BNCT facility was named Kansai BNCT Medical Center as a hub where relevant researchers can jointly carry out clinical practices.

Our Center is equipped with a cyclotron-based neutron irradiation system jointly developed by Kyoto University and Sumitomo Heavy Industries, Ltd. Our facilities are the third ones after No. 1 in Kyoto University Research Reactor Institute (renamed Institute for Integrated Radiation and Nuclear Science, Kyoto University in April 2018) and No.2 in Southern Tohoku BNCT Research Center, all of which are the only systems in the world allowing full-scale BNCT clinical practices. Currently we are conducting phase II BNCT clinical trials with boron agents manufactured by Stella Pharma Corporation. These trials have been at the final stage, so we expect that it will obtain approval within few years to make itself available for clinical practices. Also, our Center is equipped with a small cyclotron for the short-lived RI production. Along with PET facilities transferred from the university hospital, we will launch nuclear medicine services in June when the Center will start operating. In BNCT, it is necessary to determine beforehand for each patient how selectively boron agents accumulate in tumor cells and how highly they concentrate. As such we will prepare for PET with ^{18}F-labeled boron agents in the near future, but first we are implementing approved ^{18}F-FDG PET. Osaka Medical College belongs to the same incorporated educational institution as Osaka University of Pharmaceutical Sciences. So we hope to collaborate in basic research on boron agents.

Though in recent years, finally, BNCT has been widely known, there are only a small number of medical practitioners / researchers who know perfectly from the basics to clinical practices. A large gap between expectation and reality exists. The Centre, which maintains close coordination with the three universities / centers of research, also plays a role in developing human resources. Therefore we think we have great responsibility in bridging this gap.

Incomparably deeper and broader in its scientific and interdisciplinary natures than traditional radiation therapy (including proton radiation therapy and carbon-ion radiotherapy), BNCT has some characteristics enabling reaching extraordinarily high precision depending on our future research efforts. It has unlimited potential. I would ask you for your research efforts and cooperation with the Center.

Process for Japanese National Insurance Coverage of Particle Therapy

Hideyuki Sakurai
Professor and Chairman
Department of Radiation Oncology, Faculty of Medicine, University of Tsukuba

Particle therapy, the clinical study of which had started in the late 1980s, has been recognized as an advanced medical treatment in 2000s. Just around the same time, its numbers of facilities and patients have grown: there are approximately 4,500 cases of particle therapy a year at present (2,600 cases of proton therapy and 1,900 cases of heavy ion therapy, which makes 2% of the total number of the patients in radiotherapy). Currently, 12 facilities of proton therapy and 5 of heavy ion therapy are under operation in Japan. Although the implementation status and the treatment outcomes on particle therapy, including prospective study, had been published as academic papers from each facility, there were only limited numbers of studies publicized as multi-institutional joint research. Therefore, as for the insurance revision in FY 2016, Japanese Society for Radiation Oncology, with assessment by external disease-specific committees, conducted systematic reviews for childhood cancer, bone and soft tissue tumor, head and neck non-squamous carcinoma, liver cancer, and lung cancer as well as analyzed the national treatment outcomes as a retrospective study. As a result, proton therapy for pediatric tumor and heavy ion therapy for unresectable bone and soft tissue tumor have been included in the insurance coverage as of medical fee revision in FY 2016.

After that, the clinical trials for the diseases and their conditions that should particularly be focused on and evaluated, such as liver cell carcinoma and prostate cancer, have been performed as advanced medical treatment B. For advanced medical A, the society consolidated the treatment plan for specific diseases, and all the treatment facilities have uniformly been following the plan since FY 2016. By using the standardized treatment plan for all the applicable patients in every facility nationwide and by registering all the case data for analysis, the particle therapy has been carried out in the system where it can be properly evaluated.

As for the revision in FY 2018, we appealed for inclusion of particle therapy on bone and soft tissue cancer and head & neck malignant tumor (excluding squamous carcinoma in oral cavity, larynx, or pharynx) into the insurance coverage as sufficient

evidence of the effect was found, and it has been approved. We have also requested for inclusion of particle therapy for liver cancer, which was thought as a rare condition that didn't have any other radical treatment options to treat, yet it hasn't been included in the coverage at this revision. For prostate cancer, there is a variety of treatments that have reached maturity, and the methods that are safe and have high success rate on surgery and on radiotherapy have been operated. In other word, it is the category difficult to prove the superiority of particle therapy among other methods of treatment. It, however, showed satisfactory records when the data was collected from multiple facilities in the country. On the systematic review on particle therapy for prostate cancer, we found that although there wasn't any obvious evidence indicating its superiority among other advanced radiotherapies, a multitude of the treatment reports on particle therapy showed at least equal to or better outcomes than that of other therapies. In addition, it is clearly reducing radiation dosage affecting the surrounding area in fact. Meanwhile we were considering that, upon the facts found in the systematic review, particle therapy for prostate cancer should be included in the insurance coverage as early as possible to provide desirable quality of care, it has been approved at this revision in FY 2018.

Within a year and a half after the insurance revision in FY 2016, there have been 56 articles published on international journals (including 19 of multi-institutional studies), 15 articles contributed to ongoing publication, and 66 presentations in international conferences regarding to clinical results (excluding of basic researches) of Japanese treatment facilities for particle therapy. It can be said that it is the endeavor of the treatment facilities that led to this achievement that particle therapy for those diseases are now acknowledged under the insurance coverage.

Ministry of Health, Labour and Welfare: Development of evaluation index of next-generation medical devices and regenerative products —Development of the guideline on evaluating BNCT—

Junichi Hiratsuka
WG Chairman of BNCT Evaluation Working Group (WG)
Professor, Department of Radiation Oncology, Kawasaki Medical School

I was requested by editorial committee to write an article about the activity of "BNCT Assessment WG" and I would like to take this opportunity to explain it here in this NCT letter.

The objective of our activity is to develop an evaluation index to be used when PMDA assessing an accelerator-based BNCT device.

To make the reactor-based BNCT a common (standard) treatment, developing the accelerator-based BNCT device, which can be installed in medical institutions in urban area, is imperative. Currently, a clinical trial using world's first accelerator neutron source for BNCT is conducted for brain tumors and head and neck cancer and it is coming close to practical utilization. Furthermore, the Ministry of Health, Labour and Welfare designated neutron generator and boron carrier for the Sakigake Designation Scheme in 2017 and this will accelerate the movement of introducing the accelerator neutron source for BNCT into a clinical practice even more.

Considering this situation, it is an urgent issue to create an evaluation index for approval process for the acceleration-based BNCT device, which will be entered in the market in the future, even at the stage of development in order to accelerate the approval process on medical devices by PMDA. In other words, the evaluation index, which should be check by PMDA when evaluating BNCT device, is needs to be developed immediately.

In this WG, we established four task forces (TF) and investigated research and development, usage trends, and related standards on an accelerator for BNCT in and outside of Japan. We also developed the evaluation index to measure its effectiveness, safety, quality appropriately and promptly based on scientific evidences.

Summaries of four TFs discussed lately are listed below.

Full content of the report can be found on the "National Institute of Health Sciences (Evaluation WG office) website.

TF1 Investigation Report

(Research on development and usage trends in and outside of Japan and safety and performance criteria in non-clinical studies)

Hiroaki Kumada (Leader: University of Tsukuba) Masayori Ishikawa (Hokkaido University) Minoru Suzuki (Kyoto University) Hiroki Tanaka (Kyoto University) Satoshi Nakamura (National Cancer Center Japan)

We reviewed criteria required in non-clinical studies for regulatory approval for the accelerate-based BNCT device. BNCT using neutron radiation is categorized as radiation therapy. However, BNCT differs significantly from x-ray therapy or particle radiotherapy as it uses boron agents and neutron radiation. Thus, it is necessary to take its specificity into account when reviewing criteria for non-clinical studies. Also, methods to generate neutron radiation varies from the previous nuclear reactor to the accelerator method or the method using nuclear fusion reaction. In this review, therefore, we first extracted the difference between the previous external radiation method and BNCT and the specificity of BNCT and set the scope of this review. Because BNCT has complex mechanism and uses various types of neutron sources, some parts such as measurement techniques are undeveloped. For that reason, we examined technical issues and limitations and reviewed risk management. Considering these points, following criteria are established for non-clinical studies for BNCT device.

1. Differences between the previous external radiation method and BNCT, specificity of BNCT
2. Development status of BNCT device and scope
3. Current technical limitations and restrictions on BNCT
4. Risk management
5. Non-clinical studies proposal

TF2 Investigation Report

(Safety and performance criteria in clinical studies)

Minoru Suzuki (Leader: Kyoto University), Hiroshi Igaki (National Cancer Center

Japan), Shinji Kawabata (Osaka Medical College), Hideyuki Sakurai (University of Tsukuba)

BNCT system built from proton beam accelerator (including cyclotron) or target materials, which are needed for neutron generation, need to be approved in accordance with the law concerning quality, effectiveness, and securing safety (Pharmaceuticals and Medical Devices Law) for practical use. However, because the technology and therapeutic principle of BNCT does not exist in the current clinical expertise, from the stand point of effectiveness and securing safety for humans, outcome of clinical studies (meeting practice standard for clinical studies for pharmaceuticals and medical devices (GCP: Good Clinical Practice)) needed to be clarified in an application for approval.

Because pharmaceuticals (boron agents) and medical devices (neutron generator and irradiation device) are used in BNCT, it is important to plan and design a clinical trial that reflects performance of each items when implementing clinical trials. Also, setting clinical criteria reflecting performance is necessary. In this report, matters which require cautions when implementing clinical trials are established.

TF3 Investigation Report
(Radiological safety)

Yoshitomo Uwamino (Leader: RIKEN), Mitsuru Uesaka (The University of Tokyo), Shunsuke Yonai (National Institutes for Quantum and Radiological Science and Technology), Akiko Hachisuka (National Institute of Health Sciences)

Radiological safety related to following items are discussed and reported.

1. Safety of facilities
2. Safety of neutron generating target device
3. Radiation exposure of patients: normal tissues exposure
4. Radiation exposure of healthcare professionals
5. Radiation exposure of individuals who handles the accelerator and targets
6. Actions in response to additional measures for radiological protection

T4 Investigation Report
(Fundamental information for development and usage status, safety and performance of boron agents)

Hiroyuki Nakamura (Tokyo Institute of Technology)

Following items are reported.

1. Development and usages status of boron agents for BNCT
2. Need for boron element
3. Boron agents for BNCT used in the clinical study.
4. Development status of boron agents for BNCT

The evaluation index is targeting the device which its technology development is prominent and only shows the subjects that are considered important at this moment. It is subject to revision due to further technological innovation or new findings and does not have bindings on application for approval. When evaluating products targeted by the evaluation index, it is required to understand the characteristics of each product and respond flexibly based on scientific rationality. I also would like to add that other related guidelines inside and outside of the country should be used and as reference.

The 14th Congress on Neutron Capture Therapy

Chairman Yoshihiro Takai
Director of the Southern Tohoku BNCT Research Center affiliated with Southern Tohoku Research Institute for Neuroscience

The 14th Congress on Neutron Capture Therapy was held on Friday 29th September and Saturday 30th September 2017 at Koriyama View Hotel Annex located in Koriyama City, Fukushima Prefecture. The 5th BNCT Workshop (hosted by the Human Resource Development Committee of the Japanese Society of Neutron Capture Therapy and supported by this Congress) was held on 28th September, the day before the Congress, together with a facility tour of Southern Tohoku BNCT Research Center. Eighty-nine participants observed the world's first BNCT therapy facility annexed to a general hospital.

Two hundred fifty-one participants (103 regular members, 129 non-members, 19 students) joined the Congress and hot discussions were made in the fields of physics, pharmacy & chemistry, clinical medicine & technology, and biology. Thank you for your participation.

Symposium

The accelerator BNCT system which is installable in hospitals was introduced in Kyoto University Research Reactor Institute and Southern Tohoku BNCT Research Center. Phase II Clinical Study has been conducted for malignant brain tumor at both institutions since January 2016 and for recurrent and advanced head and neck cancer at Southern Tohoku BNCT Research Center since July 2016. Regulatory application is expected to be made in the near future. Having proceeded to such stage of development, it is important for Japan to transmit information on clinical techniques of the accelerator BNCT in order to have it recognized as a clinical therapy and to have it used worldwide.

For this purpose, the theme of this Congress was decided as "Issues toward the

realization of clinical practices using accelerator-based BNCT". Various discussions were made mainly at the symposium concerning issues that may be solved by analyses of a large amount of clinically obtained data, physico-technical issues including setup of patients and issues on nursing for BNCT. The future direction to be taken from the aspect of clinical medicine has been indicated. Moreover, the issue on radiation exposure by BNCT was raised and the low exposure dose of BNCT compared to the conventional therapies such as X-ray therapy was reported.

The numbers of the lecture themes were 57 in total, consisting of 1 special lecture, 1 educational lecture, 2 symposium lectures (6 lecturers, 1 discussant), 2 luncheon seminar lectures, 36 general presentations and 15 poster sessions.

Poster Session

Contribution of Japan in the BNCT research and new analysis of the CBE factor, presented by the invited lecturers, were very meaningful for all researchers engaged in BNCT. General presentations were made in 4 fields; physics, pharmacology & chemistry, clinical medicine & technology, and biology. Development of equipment, new drugs, technological improvement at clinical sites and biological issues on the effectiveness of BNCT were presented, each showing further progress compared to last year. These presentations, including questions and answers, ended in a great success.

Public program was jointly organized with the Association for Nuclear Technology in Medicine. Two lectures and one special lecture were held. Dr. Katsumi Hirose of the Southern Tohoku BNCT Research Center and Dr. Masao Murakami of the Proton Therapy Center presented clear expositions of BNCT and proton therapy. Mr. Shuntaro Torigoe, a journalist, was invited for a special lecture with the theme "Living with Cancer". 310 citizens listened to the lecture with deep concern and many questions were raised.

Party after the Congress

Finally, I would like to express my appreciation to Prof. Hiroyuki Nakamura, the

President of the Japanese Society of Neutron Capture Therapy, Prof. Hironobu Yanagie, the Chairman of the previous Congress and the members of the Society for their various fruitful advice, and to the staff of the management secretariat for their valuable efforts made for the management and practical business for this Congress.

For further details of this Congress, please refer to the "Information on Nuclear Technology in Medicine" Vol. 18 issued by the Association for Nuclear Technology in Medicine.

Report on the 9th Young Researchers BNCT Meeting (YBNCT9)

Yoshinori Sakurai
Chairman of the Organizing Committee
Associate Professor, Institute for Integrated Radiation and Nuclear Science, Kyoto University

The 9th Young Researchers BNCT Meeting (YBNCT9) was held for 3 days from November 13th to 15th 2017 or for 7 days from November 11th to 17th including the tightly-scheduled "Dan-Gun (bullet) tour". The Young Researchers BNCT Meeting (YBNCT) has been held every 2 years since 1999 between the International Congress on Neutron Capture Therapy (ICNCT), mainly aiming at young researchers engaged in various researches in relation with BNCT. The 9th Meeting was the first meeting held in Japan in 18 years of its history. It was operated in the "all-Japan" system with the Kyoto University Research Reactor Institute(KURRI) (current name; Institute for Integrated Radiation and Nuclear Science, Kyoto University) as a meeting steward.

On the 1st day, in November 11th, the observation tour of the Southern Tohoku BNCT Research Center was held as the first stage of the "Dan-Gun tour" which was the big attraction of this meeting. Although there were concerns that foreign participants might feel that it was a vault to a challenging place, 17 participants joined the tour which was as generally planned. We would like to express our appreciation to Dr. Katsumi Hirose, Dr. Takaomi Harada and other staff of the Research Center.

On the 2nd day, in November 12th, the observation tour of the Kyoto University Research Reactor Institute was held as the second stage of the "Dan-Gun tour" with 41 participants. At the same time a "Workshop on International Joint Research" was held and active discussions were made on the international joint research using Kyoto University Research Reactor (KUR). After the workshop, the participants moved to Kyoto by a chartered bus with the staff of the Institute. That night, the members deepened friendship at a Japanese bar restaurant near Kyoto Station.

On the 3rd to 5th day, from November 13th to 15th, the Meeting was held at the Obaku Plaza on Uji Campus of Kyoto University. Since this Meeting is mainly for young researchers, the program was entirely composed of giving research presentations with no special lecture. A total of 94 presentations were made comprising 53 oral presentations and 41 poster presentations. It was a successful meeting beyond expectation. A total of 161 participants from 16 countries joined the meeting during

these three days. It is assumed to be the record number of participants among the previous meetings. Almost half of them were from overseas. I would like to thank Ms. Reiko Matsuoka for her help in the reception.

We lined up a number of awards to encourage young researchers this time. 16 young researchers were awarded; 5 for the Kent Riley Award which was newly established in the last meeting, 5 for the Best Presentation Award and 6 for the Best Poster Presentation Award. Moreover, apart from the awards, 7 young researchers were offered travel grants. We extend our gratitude to the Kyoto University Foundation, the Japanese Society of Neutron Capture Therapy and other enterprises for their support for these awards and travel grants.

On the 6th day, in November 16th, the observation tour of the National Cancer Center Japan was held as the third stage of the "Dan-Gun tour". We needed to conduct the tour smoothly since we only had time allowed for the tour at lunch break from 12:00 to 13:00, therefore, two graduate students from the Graduate School of Engineering, Kyoto University were sent as tour conductors for the third and fourth stages of the "Dan-Gun tour". 45 participants, which was the largest number of participants among the stages of the "Dan-Gun tour", joined this observation tour. We extend our gratitude to Dr. Hiroshi Igaki, Dr. Satoshi Nakamura and the staff of the Center.

On the 7th day, in November 17th, the observation tour of the Ibaraki Quantum Beam Research Center was held as the fourth stage of the "Dan-Gun tour". 34 participants joined the tour. We extend our gratitude to Prof. Hiroaki Kumada and Prof. Teruhito Aihara of Tsukuba University and the staff of the Center. We also appreciate Mr. Naonori Ko and Mr. Keita Okazaki, the graduate students of Kyoto University, for their support as tour conductors. I remember I realized the completion of the YBNCT9 when Prof. Kumada reported me that the tour had ended.

We got cooperation from many people for holding the YBNCT9 and would like to reiterate our gratitude to the staff of the YBNCT9 Organizing Committee. We extend our appreciation especially to Ms. Maki Nakatani of BNCT Promotion Office in Kyoto University Research Reactor Institute, for her dedication to the general clerical work, venue establishment and reception work for the Meeting. Finally, we would like to express our sincere gratitude to all participants, especially to participants from overseas. For those who fully participated the scheduled events, the whole travel distance during the seven days in Japan were about 1,500 km at the shortest, starting and ending at Narita; Narita→Koriyama→Kumatori→Uji→Tokyo→Tsukuba→Narita. Thank you all for your participation.

"Bullet tour" 2nd stage-Kyoto Univ. Research Reactor Institute

Deepening friendship at Kyoto

Group photo of the Meeting

Award ceremony

Notice on the 15th Congress on Neutron Capture Therapy

President Masayori Ishikawa
Professor, Faculty of Health Sciences, Hokkaido University

"The 15th Congress on Neutron Capture Therapy" will be held at the Hokkaido University Conference Hall on September 1st (Sat) and 2nd (Sun) 2018. This is the 15th Congress since the foundation of the research meeting and it is my great honor to be appointed a chairman of the Congress when its scale is growing gradually and steadily. All the staff of the Organizing Committee is proceeding with the preparations to make the Congress fruitful and successful, with reference to the previous congresses.

Boron Neutron Capture Therapy (BNCT) is now making a transition from irradiation based on research reactor to irradiation using accelerator-based neutron source and that may enable much more facilities to provide BNCT. The quality of the therapy has been secured by choosing the best therapy through trial and error for each case, however, to enable equivalent therapy to be provided by the facilities which are assumed to increase in the future, it is essential to share the consensus on the base technology and to establish the process of quality management/quality assurance of BNCT.

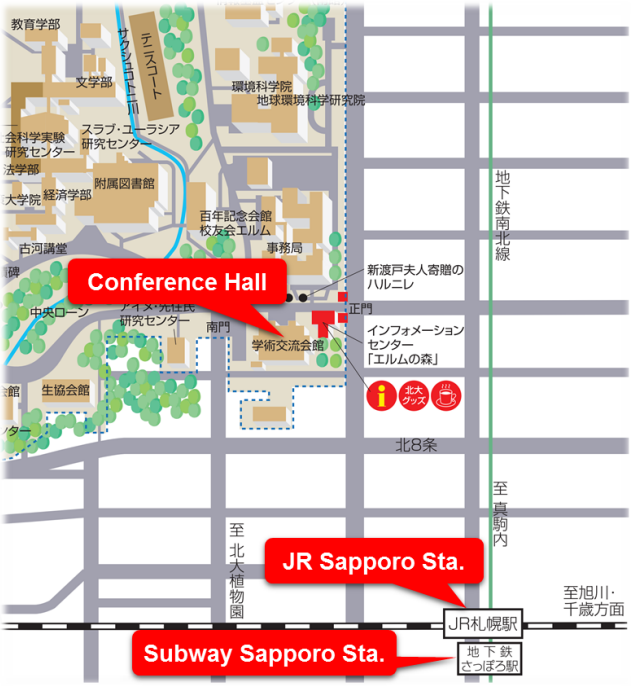
For that purpose, the 15th Congress will be held with the theme "Establishing the Base Technology to Improve the Quality of the Therapy". BNCT is generally categorized into three fields; medicine & biology, physics & engineering and chemistry & pharmacology. The established technologies and technologies that still need to be discussed are mixed in each field. In the field of medicine & biology, careful discussion is necessary on prescribed dose and normal tissue tolerance dose in association with expanding the applicable diseases and devising the irradiation methods. In the field of physics & engineering, the appearance of irradiation facilities using accelerator-based neutron source raises the need to establish technologies for defining and controlling precise neutron irradiation levels. In the field of chemistry & pharmacology, establishment of methods for quantitative rating of drug accumulation in tumors are the critical issue, as well as the new drug development. In the 15th Congress, the program is organized to enable enough time for discussions, including symposiums to discuss the above mentioned issues, luncheon seminars to introduce new technologies and general

lectures in oral and postal forms. We expect active discussions by all participants. The 6th BNCT Workshop is also scheduled at the same venue on the day before the 15th Congress.

The Congress will take place in Hokkaido University surrounded by rich nature. Taking a walk in the campus may give you a refreshing feeling. We hope you enjoy the cool climate of Sapporo in the season when it may still be hot outside Hokkaido. Sapporo is also rich in foodstuffs, so have a nice time with delicious foods during your stay. We welcome you all and hope the Congress would be fruitful and successful.
Website URL: http://jsnct15.unim.jp

Date : September 1st (Sat) - 2nd (Sun) 2018

Place: Hokkaido University Conference Hall (Sapporo)



[Access]

5-minute walk from
JR Sapporo Station

8-minute walk from
Subway Sapporo Station

[From airport]

JR rapid service
35 min to Sapporo Station

Odori park

Sapporo clock tower

Sapporo Nijo market

Sapporo Sweets cafe

Concert hall 'Kitara'

Chitose Sake museum

Nakashima park

JR tower view (T38)

18th International Congress on Neutron Capture Therapy

October 28 - November 2, 2018 TAIPEI, TAIWAN

歡迎光臨・Welcome・ようこそ

Welcome Message

Dear Colleagues,

We are pleased to invite you to attend the 18th International Congress on Neutron Capture Therapy (ICNCT-18) to be held in Taipei, Taiwan, from October 28 to November 2, 2018.

The conference will offer the opportunity to meet and interact with multi-disciplinary experts in Neutron Capture Therapy (NCT), and present the latest clinical and basic research results in the treatment of cancer using NCT. Various groups related to NCT worldwide have reported significant developments in clinical matters, radiation biology, chemistry & pharmacology, physics & engineering, and boron determination & imaging technology in recent years. Boron Neutron Capture Therapy (BNCT) had been used globally in clinical trials to treat patients with a variety of cancers, such as head and neck, melanoma, brain, and liver cancers. In Taiwan, our BNCT team has treated head and neck tumors and brain tumors, as well as developing a new boron drug for treating liver cancer. During ICNCT-18, the promising clinical results from our team will be presented, along with the encouraging results of NCT around the world.

The international conference is composed of world-renowned scientists from industry and academia, working together on the goals of cancer treatment. Clinicians and researchers from around the world will meet in ICNCT-18 to show their findings and generate new thought in the field of NCT. Many excellent papers and constructive discussions at the conference are expected, which will greatly promote the continuous development of NCT. Thus it is my great pleasure to invite colleagues in all professions related to NCT to the ICNCT-18.

We warmly welcome you and your team and hope that you will all enjoy the conference in Taiwan's beautiful scenery and pleasant climate.

With Best Regards,

Fong-In Chou

Fong-In Chou, President
18th ICNCT congress
International Society for Neutron Capture Therapy

Attractions in Taiwan

Tsing Hua Open-pool Reactor (THOR)

Taipei Veterans General Hospital

Important Dates

Website Launch
December 1, 2017

Abstract Submission Starts
January 15, 2018

Early-bird Registration Starts
April 15, 2018

Abstract Submission Closes
April 15, 2018

Notification of Abstract Review Results
May 31, 2018

Early-bird Registration Closes
June 30, 2018

Last Day for Cancellation of Registration with 75% Refund
July 31, 2018

On-line Registration Closes
September 30, 2018

Call for Paper
論文募集

The ICNCT-18 cordially invites and welcomes you an abstract(s) for poster or oral presentation(s) to the field in the following scientific categories：

Categories:

- Clinical matters
- Radiation biology
- Chemistry & Pharmacology
- Physics & Engineering
- Boron determination & Imaging technology
- Others

http://www.icnct18.org

18th International Congress on Neutron Capture Therapy

October 28 - November 2, 2018 TAIPEI, TAIWAN

Program at-a-glance (Tentative)

18th Internaional Congress on Neutron Capture Therapy 2018
Tentative Program

Time/Date	October 28, 2018 Sunday	October 29, 2018 Monday	October 30, 2018 Tuesday	October 31, 2018 Wednesday	November 1, 2018 Thursday	November 2, 2018 Friday
08:00-08:30						
08:30-09:00						
09:00-09:30	09:00-14:00 Training Course	08:30-17:30 Registration; 09:00-09:30 Opening Ceremony	08:30-17:30 Registration; 09:00-10:00 Plenary Lecture	08:30-12:00 Registration; 09:00-10:00 Plenary Lecture	08:30-17:30 Registration; 09:00-10:00 Plenary Lecture	09:00-10:00 Plenary Lecture
09:30-10:00		09:30-10:00 Hatanaka Award				
10:00-10:30		10:00-10:30 Coffee Break	10:00-10:30 Coffee Break	10:00-10:30 Coffee Break	10:00-10:30 Coffee Break	10:00-10:30 Coffee Break
10:30-11:00		10:30-12:00 Parallel Sessions	10:30-12:00 Parallel Sessions	10:30-12:00 Parallel Sessions	10:30-12:00 Parallel Sessions	10:30-11:30 Parallel Sessions
11:00-11:30						
11:30-12:00						11:30-12:00 Closing Ceremony
12:00-12:30		12:00-13:30 Lunch Luncheon Seminar	12:00-13:30 Lunch Luncheon Seminar	12:30-18:00 Technical Tour to THOR	12:00-13:30 Lunch Luncheon Seminar	12:00-13:00 Executive Board Meeting and Lunch
12:30-13:00						
13:00-13:30						13:00-18:00 Optional Tour
13:30-14:00		13:30-14:30 Invited Lecture	13:30-15:00 Plenary Lecture		13:30-15:00 Plenary Lecture	
14:00-14:30	14:00-19:00 Registration					
14:30-15:00	14:30-15:30 Executive Board Meeting	14:30-16:00 Plenary Lecture				
15:00-15:30			15:00-16:30 Parallel Sessions & Coffee Break		15:00-16:30 Parallel Sessions & Coffee Break	
15:30-16:00	15:30-16:00 Board of Councilors					
16:00-16:30		16:00-16:30 Coffee Break				
16:30-17:00		16:30-18:00 Parallel Sessions	16:30-18:00 Parallel Sessions		16:30-18:00 Parallel Sessions	
17:00-17:30	17:00-19:00 Welcome Reception					
17:30-18:00						
18:00-18:30						
18:30-19:00				18:30-20:30 Congress Banquet		
19:00-19:30						
19:30-20:00						
20:00-20:30						
20:30-21:00						

Registration Fee

Participants are encouraged to register as early as possible to take advantage of discount fee. (Early-bird Registration Starts from April 15, 2018 through the on line registration system.)

18th International Congress on Neutron Capture Therapy 2018 Registration Fee

Category	Early Bird	Regular	On!site
Deadline (GMT+8)	June 30, 2018	Sep. 30, 2018	Oct.28-Nov.2, 2018
Member	NT19200≒USD 600	NT20800≒USD 650	NT22400≒USD 700
Non-member	NT22400≒USD 700	NT24000≒USD 750	NT25600≒USD 800
Student	NT10400≒USD 325	NT12000≒USD 375	NT13600≒USD 425
Accompanying Person	NT9600≒USD 300		
Congress Tour	NT2240≒USD 70		

Organizer:

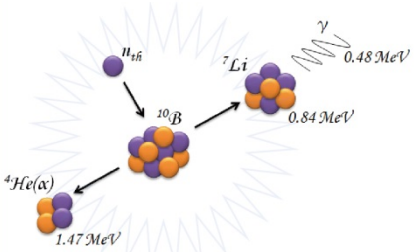
National Tsing Hua University

Taipei Veterans General Hospital

Taiwan Society of Neutron Capture Therapy

Theme:

Precision Therapy, Beautiful Tomorrow – We Here, We Care.



Boron neutron capture reactions

Venue

CHANG YUNG-FA FOUNDATION
International Convention Center

Conference venue is located on Zhongshan South Road, an easily accessible thoroughfare. The building faces the Ketagalan Boulevard and is close to the National Taiwan University Hospital and Liberty Square (Chiang Kai-shek Memorial Hall). It is a 5 min walk from MRT National Taiwan University Hospital Station and a 5min drive from Taipei Main Station.

Add: No.11, Zhongshan S. Rd., Taipei City 10048, Taiwan
Tel: +886(2)2351-6699 Fax：+886(2)2351-5176

http://www.icnct18.org

The Best Presentation Award of the 14 th annual meeting of Japan society for Neutron Capture Therapy

Accelerator-Based BNCT System at Nagoya University
- Development of a Sealed Li Target -

Sachiko Yoshihashi
Department of Energy Science and Engineering, Nagoya University

1. Introduction

An accelerator-based neutron source for BNCT is currently under development with a combination of a DC accelerator and a compact sealed lithium (Li)target in Nagoya University. Proton beam of 2.8 MeV and 15 mA (42 kW) ejected from a Dynamitron accelerator will be injected to the Li target. Low energy proton beam incident of Li target is one of the most suitable reactions for accelerator-based BNCT system, because a sufficient flux and good quality of epi-thermal neuron beam can be obtained by using a compact beam shaping assembly (BSA), and also the radiation exposure of medical staffs can be reduced by lowering the activation of accelerator facility. However, metallic Li has several difficulties in chemical properties (low melting point, high chemical activity, and Be-7 production) as target materials. For resolving those issues, we are developing a compact sealed Li target.

2. The progress of accelerator and beamline

In August 2017, we completed the installation of the beamline and confirmed the proton beam with an energy of 2.8 MeV and a current of 2 mA can be transmitted to the target position. Beam profile was obtained using a beam profile monitor installed on the beamline and the stability of the proton beam was confirmed.

3. Development of sealed Li target

A thin Li layer (0.14 mm) is set on the embossed structure of a tantalum plate and covered by thin titanium (Ti) alloy foil to confine liquid Li and radioisotopes (Be-7 or tritium) in the target. A proton beam of 42 kW will irradiate the Li through the Ti foil (irradiation area: 80 x 80 mm^2). A new cooling system with a strong turbulent flow in the water channels induced by the V-shaped staggered rib structure was developed to remove the high heat load from the target. Heat removal experiments were performed

by utilizing an electron beam in the Active Cooling Test Stand 2 (ACT2) at National Institute for Fusion Science (NIFS). In the experiments, we had confirmed the new cooling system could remove the high heat load of 42 kW, efficiently. Based on the result of the heat removal test, we had estimated the surface temperature of the Ti is about 160 degree C, when the heat load of the proton beam is 6.6 MW/m^2. In the estimation, we assumed a good heat transfer rate between the Ti foil, the Li metal and the target base plate, based on a mockup test about the wettability between those metals.

4. Conclusion

In the next step, we will confirm the endurance of the sealed Li target of the proton beam and prepare for the In-vitro test.

The Best Presentation Award of the 14 th annual meeting of Japan society for Neutron Capture Therapy

Title Development of disulfide-bridged boron cluster maleimide (SSMID) and identification of its conjugation site on albumin

Satomu Ishii, Shinichi Sato, Hiroyuki Nakamura
Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology

For the treatment of cancer where *p*-boronophenylalanine (BPA) does not accumulate and is not effective for BNCT, development of methods for selectively and efficiently delivering boron to various types of cancer based on the different uptake mechanism from BPA is required. We focused on serum albumin which is known to selectively accumulate in tumors using the enhanced permeability and retention (EPR) effect as a boron delivery carrier and has developed maleimide-functionalized *closo*-dodecaborate (MID) as a reagent for binding boron cluster to albumin. Boron cluster-conjugated albumin can be readily prepared using MID. When MID-conjugated albumin was administered to tumor bearing mice, high efficiency boron delivery to tumor tissues was achieved 12 hours after drug administration in the 30 mg [B] / kg administration group.[1]
It is generally known that the maleimide group selectively binds only with free cysteine residues under physiological conditions. Although albumin has only one free cysteine residue, Cys34, western blotting and inductively coupled plasma (ICP) analysis revealed that multiple MID molecules bind to one molecule of albumin. These results suggested that MID may bind to amino acid residues other than Cys34. Therefore, MS/MS analysis was attempted in order to identify the modified site of MID. However, due to the negative charge of the boron ion cluster, it was difficult to identify the modified site.
For the purpose of identifying the modified site of MID in this study, a compound named SSMID, having a disulfide bond in the linker structure of MID, was newly synthesized. By reducing the disulfide bond in SSMID-conjugated albumin, the negatively charged cluster was cleaved and an ionizable peptide derived from the SSMID binding site were obtained. MS/MS analysis by liquid chromatography-matrix-assisted laser desorption/ionization mass spectrometry (LC-MALDI) revealed that SSMID binds to at least three amino acid residues besides

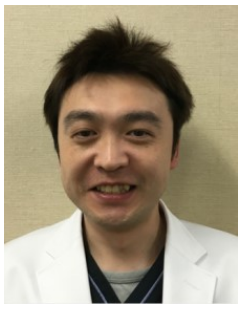
the free cysteine residue (Cys 34). From the information on identified binding sites, it was revealed that MID binds to drug binding sites in albumin, promoting the formation of bonds with amino acid residues in proximity to drug binding sites.

Finally, we would like to thank Prof. Yoshihiro Takai, the chairperson of the 14th Japan BNCT conference, the secretariats and the referee of this best presentation award. We also would like to thank Dr. Itsuro Kato who gave us the opportunity to publish our findings in NCT Letter.

【reference】

1. S. Kikuchi, D. Kanoh, S. Sato, Y. Sakurai, M. Suzuki, H. Nakamura, *J. Control. Release* **2016**, *237*, 160–167.

The Best Presentation Award of the 14th annual meeting of Japan society for Neutron Capture Therapy



The effective field size in depth allowed with the mucosal dose constraint in head and neck BNCT

Katsumi Hirose[1], Kazuhiro Arai[1], Takaomi Harada[1], Tomoaki Motoyanagi[1], Hidehiko Takeuchi [1], Ryohei Kato[1], Takahiro Kato[1], Yoshihiro Takai[1]

[1]Southern Tohoku BNCT Research Center

In boron neutron capture therapy, thermal neutron flux peaks at a depth of about 2 cm and then decreases according to the depth of the tissues. Therefore, the field with treatable level of neutron flux is limiting. Especially in the head and neck cancer, treatment time and prescribed dose are often passively determined depending on the tolerable dose of the oral and pharyngeal mucosa. However, the anatomical structure of mucosa is very complicated and there is a risk that delineation of mucosa will be performed with less reproducibility. As a result, the validity of adopting mucosal dose as a prescribe dose is missing. However, there is no consensus of methodology for delineating mucosa, and furthermore, the detailed way of delineation has not been presented in reported clinical trials. Therefore, in this study, we investigated the impact of tumor localization on treatable field size of BNCT based on dose prescription passively defined by mucosal tolerable dose in the patients with a head and neck cancer.

Fourteen patients with newly diagnosed/recurrent head and neck cancer who received prior radiotherapy were enrolled. Treatment plan for sitting-positioned BNCT with CT datasets taken at past treatment plan were re-performed assuming treatment for tumor recurrence. Using treatment planning system SERA, delineation of organs including oral and pharyngeal mucosa was performed on past treatment plan CT integrated with MRI GdT1-weighted images or STIR images. Patients were fixed with position optimized with neutron beam setting. Prescribed dose for tumor was calculated as the maximal dose of mucosa was given 12 Gy-Eq with adoption of a fixed T/B ratio of boron as 3.5 and a blood boron concentration as 25 ppm. Tumor dose distribution on the beam axis was decided and the region with ≥20 Gy-Eq as tumor dose was regarded as treatable field, and depth and width of the field size were evaluated.

The results of evaluation of the treatable field size were depicted in Figure 1. Oral cavity cancers had short treatment time and resulting tendency with field size

narrowing. On the other hand, tumors located apart from oral cavity, such as orbital, parotid gland, maxillary, and nasal cavity cancer had comparative wide treatable field size.

In this investigation, tolerance dose of mucosa was set as 12 Gy-Eq. It should be elucidated how to define the delineation of mucosa in past clinical studies of BNCT and the true tolerable dose for mucosa should be re-evaluated based on a newly standardized delineation method of mucosa from the past clinical studies.

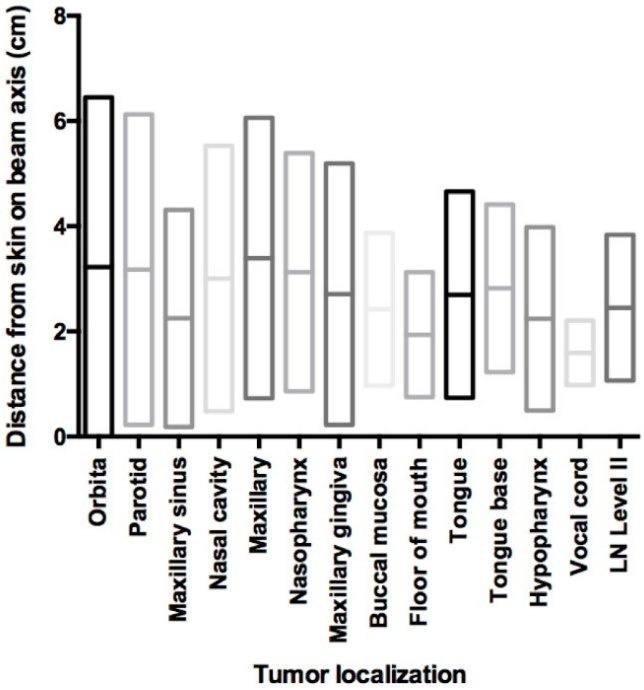


Fig 1. **The size in depth of effective treatment field with 20 Gy-Eq-over tumor dose calculated from tumor dose distribution on the center of the beam axis** CTV margin (5 mm) and setup margin (3 mm) were excluded from effective treatment field size.

Finally, I would like to express my gratitude to Dr. Itsuro Kato for giving me an opportunity to introduce my presentation at this Newsletter.

Article-introduction of the topic

1. <Physics >

Title: Development of An Epi-thermal Neutron Field for Fundamental Researches for BNCT with A DT Neutron Source

Authors: Yuta Osawa, Shoichi Imoto, Sachie Kusaka, Fuminobu Sato, Masahiro Tanoshita and Isao Murata

The source: EPJ Web of Conferences 153, 04008, 2017

http://www.epj-conferences.org/articles/epjconf/pdf/2017/22/epjconf_icrs2017_04008.pdf

Presented by **Shingo Tamaki** (Graduate School of Engineering, Osaka University)

2. <Physics >

Title: BGO as a hybrid scintillator/Cherenkov radiator for cost effective time-of-flight PET

Authors: S.E. Brunner and D.R. Schaart

The source: Physics in Medicine & Biology (2017) 62: 4421-4439

http://iopscience.iop.org/article/10.1088/1361-6560/aa6a49/pdf

Presented by **Tatsushi Shima and Ryoichi Seki** (Research Center for Nuclear Physics Osaka University)

3. <Pharmacology>

Title: Comparison of the pharmacokinetics between L-BPA and L-FBPA using the same administration dose and protocol: a validation study for the theranostic approach using [^{18}F]-L-FBPA positron emission tomography in boron neutron capture therapy

Authors: Tsubasa Watanabe, Yoshihide Hattori, Youichiro Ohta, Miki Ishimura, Yosuke Nakagawa, Yu Sanada, Hiroki Tanaka, Satoshi Fukutani, Shin-ichiro Masunaga, Masahiro Hiraoka, Koji Ono, Minoru Suzuki and Mitsunori Kirihata

The source: BMC Cancer (2016) 16:859

https://repository.kulib.kyoto-u.ac.jp/dspace/bitstream/2433/218460/1/s12885-016-2913-x.pdf

Presented by **Yoshihide Hattori** (BNCT Research Center,

Osaka prefecture University)

4. <Biology>

Title: Abscopal effect of boron neutron capture therapy (BNCT): proof of principle in an experimental model of colon cancer

Authors: Verónica A. Trivillin, Emiliano C. C. Pozzi, Lucas L. Colombo, Silvia I. Thorp, Marcela A. Garabalino, Andrea Monti Hughes, Sara J. González, Rubén O. Farías, Paula Curotto, Gustavo A. Santa Cruz, Daniel G. Carando, Amanda E. Schwint

The sources: Radiation and Environmental Biophysics (2017) 56(4):365-375

https://link.springer.com/content/pdf/10.1007%2Fs00411-017-0704-7.pdf

Presented by **Yu Sanada** (Particle Radiation Biology, Division of Radiation Life Science, Kyoto University Institute for Integrated Radiation and Nuclear Science)

Editor's Postscript

On the Publication of NCT letter Vol. 5

Chief Editor of NCT letter
Itsuro Kato
The 2nd Department of Maxillofacial Surgery, Graduate School of Dentistry, Osaka University

I would like to take this opportunity to wish every success to all of the members of the Japanese Society of Neutron Capture Therapy. I took over the role of the chief editor from Dr. Teruyoshi Kageji at the board meeting of the Society held on September 30th, 2017. The members I worked with for the NCT letter were Prof. Mitsuko Masutani of the Department of Frontier Life Sciences, Nagasaki University Graduate School of Biomedical Sciences and Dr. Teruyoshi Kageji of the Department of Neurosurgery, Tokushima Prefectural Kaifu Hospital as editors and Prof. Hideki Matsui of the Department of Physiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences as an advisor. The NCT letter Vol. 5 was published, seeking advice from Prof. Hiroyuki Nakamura, the president of this Society, although behind schedule.

As described in the feature article written by Dr. Hideyuki Sakurai, particle radiotherapy is now covered by insurance also for malignant head and neck tumors (excluding oral and laryngopharyngeal squamous cell carcinoma). As a result, proton beam therapy currently has little difference with IMRT in therapy cost, giving patients free choice of therapy.

On the other hand, in the field of "immunotherapy", long-term surviving cases were determined in the clinical trial for treatment of advanced cancer in various areas using immune checkpoint inhibitors, therefore, malignant melanoma, non-small cell lung cancer, head and neck cancer and gastric cancer have been included in the insurance coverage in succession. On the contrary, the "immune cell therapy" of which medical expenses have not been covered by insurance and thus is a high-cost therapy is showing signs of decay.

As to the current situation of BNCT, Phase II study has completed using accelerator BNCT for recurrent head and neck cancer and brain tumor at the Institute for Integrated Radiation and Nuclear Science, Kyoto University and the Southern Tohoku Hospital.

Hereafter, the treatment results in Phase III study will be the “key” point. In the future, proton beam therapy and immune checkpoint inhibitors are expected to be therapies comparable to BNCT, depending on the area.