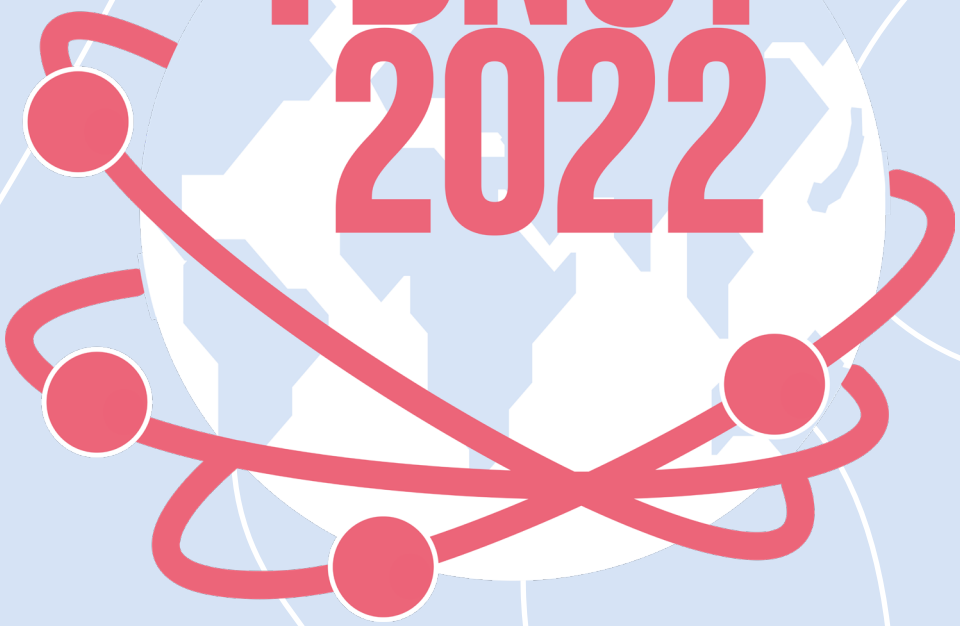
YOUNG RESEARCHERS' BNCT MEETING | VIRTUAL CONGRESS | 14-18 NOV 2022

YBNCT 2022



NO FRONTIERS IN BNCT

INTERNATIONAL SOCIETY FOR NEUTRON CAPTURE THERAPY

CONTENTS

YBNCT 2022

WELCOME

With great pleasure, the Communication Task Force (CTF) of the International Society for Neutron Capture Therapy (ISNCT) invites you to the Young Researchers' Meeting 2022 – hosted by CTF, to be held virtually between November 14th and 18th.

As you may know, the Young BNCT Meetings are biennial multinational conferences focused on the activities of early-career researchers and students, that seek to provide an environment that encourages communication and collaboration among all scientists involved in NCT worldwide. The CTF had previously established some guidelines for these meetings. This year, the Executive Board of the ISNCT asked the CTF to organize the Young Researchers' BNCT meeting in 2022. This is the first time that the scientific conference will be hosted virtually by an international network, the CTF of the ISNCT, rather than by a specific country.

Under the motto No frontiers in BNCT, in this "YBNCT 2022 - CTF edition" we expect an easy-going, inclusive, interactive and high-quality congress, focused on early-career researchers. YBNCT2022 - CTF edition seeks to gather young scientists presenting their ongoing work in BNCT. We hope the participation of experienced researchers through lectures, abstract reviewing, chairs and contributions in the audience guarantees a high-quality outcome.

We are facing a new era of BNCT, with multiple centers being installed and already treating patients. In the context of this transformation, new researchers play a major role in addressing cutting-edge challenges. This congress is a unique opportunity to gain experience sharing results and networking with colleagues all over the world.

With more than 250 participants from all over the world, around 100 contributions, 5 educational sessions and at least 2 social events, we expect this conference to be a success! Our partner, Virtual Chair, has devoted hours of work to create an innovative virtual venue that reflects the spirit of young researchers.

We want to thank the members of our committees for the work already devoted and still to come. We also want to express our appreciation to our sponsors, who made this event possible. Please visit our sponsor's booths in our conference main lobby! This project could not have been done without the continuous support and trust of the authorities of the International Society for Neutron Capture Therapy (ISNCT). The officialization of the ISNCT has played a pivotal role to manage the organization of this conference. And for us, the Communication Task Force, this opportunity has led us to a new level of organization and friendship.

Welcome to the YBNCT-2022, CTF edition.
We hope you enjoy the conference!

Agustina Portu - President
María Pedrosa Rivera - Secretary
Setareh Fatemi - Secretary
On behalf of the CTF of the ISNCT

ABOUT ISNCT

Founded in 1983, The International Society for Neutron Capture Therapy is a multidisciplinary nonprofit professional and educational association that aims to facilitate the continued development of Neutron Capture Therapy, as a nuclear medical procedure for treatment of some of the most serious forms of cancer. You can find more information at isnct.net.

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The Communication Task Force

The Communication Task Force is an official organ of the ISNCT, formed by volunteer members. Since 2020, the CTF has been working methodically and continuously with the mission of contributing to communication and ISNCT outreach and to create and maintain a communication system with the public.
We invite you to read more content on our website, newsletters and social networks.

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CONGRESS COMMITTEES

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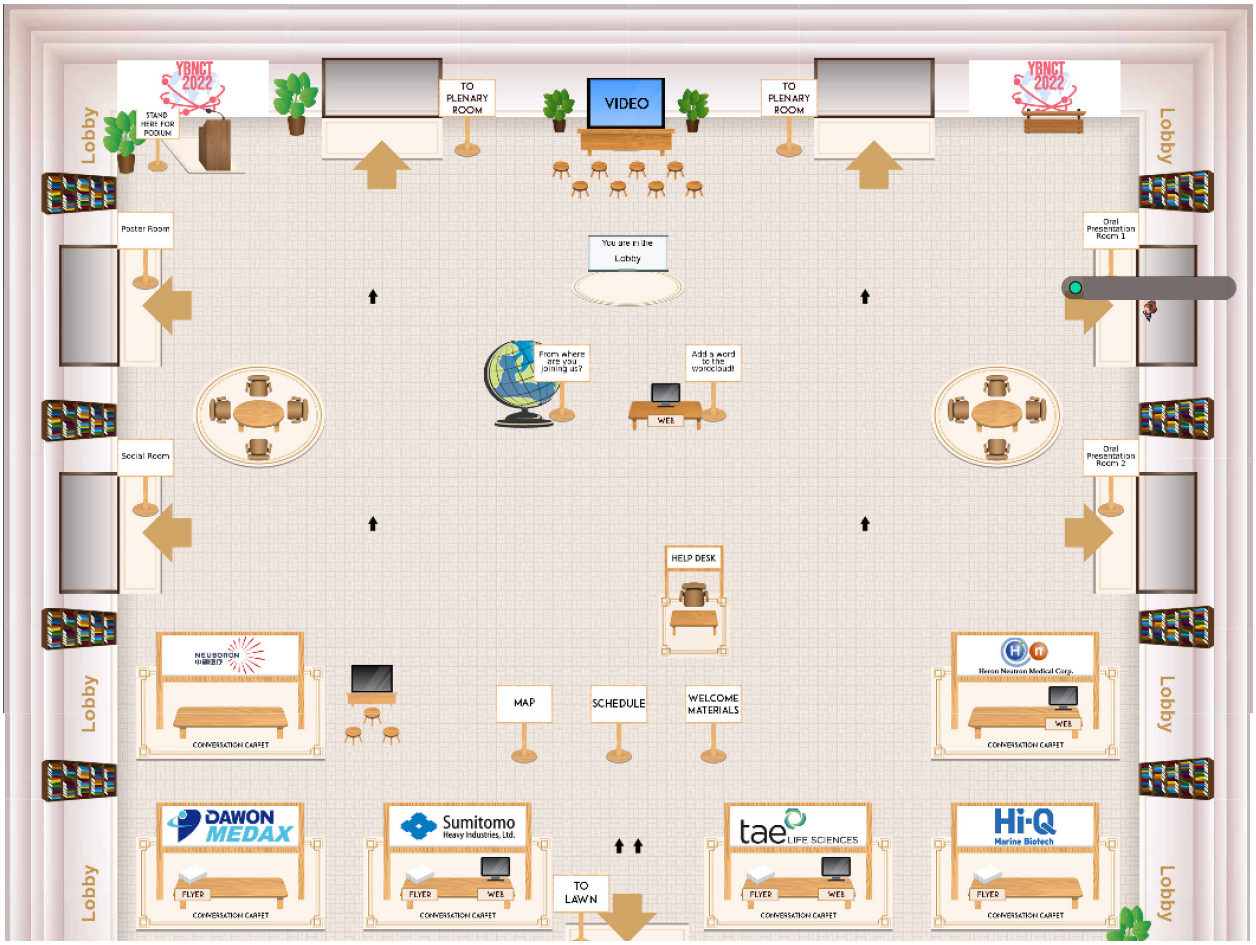
CONGRESS VENUE

As the YBNCT is focused on young researchers, we would like to create a friendly and easy-going environment, assuring as much interaction between participants as possible, despite the virtual nature of the congress. Virtual Chair creates metaverses in which to organize interactive conferences, allowing the users to experience social interactions in the virtual settings as natural as in real-life events.

Link to Virtual Venue

https://www.virtualchair.net/events/ybnct-2022



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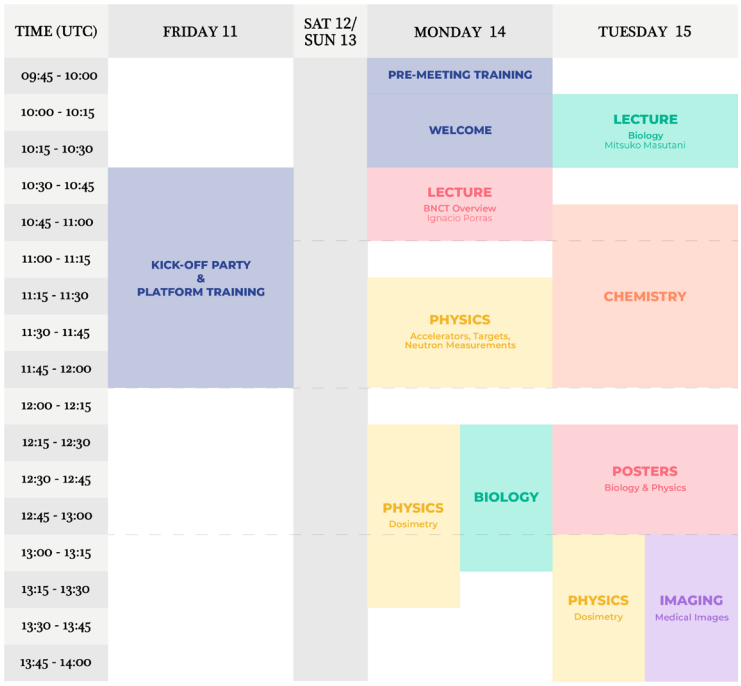
SCHEDULE

The meeting will be held virtually between November 14th and 18th, from 10:00 to 14:00 UTC (Coordinated Universal Time).



PROGRAM

DAILY PROGRAM

DAY 1 - 14TH NOVEMBER - 10:00-14:00 UTC

9:45 UTC - Pre-Meeting Training (Plenary room)

10:00-10:30 UTC - **Welcome**: CTF welcome, ISNCT president words, sponsors announcement (Plenary room)

10:30-11:00 UTC - **Educational Lecture 1, BNCT Overview** (Plenary room), "*BNCT overview and opportunities*"
Ignacio Porras, *Department of Atomic, Molecular and Nuclear Physics, University of Granada, Spain*
[Chairs: Akira Matsumura and Agustina Portu]

11:00-11:15 UTC - Break

11:15-12:00 UTC - **Talks 1, Physics: Accelerators&NeutronMeasurements** (Room 1)
[Chairs: Alex Makarov and Hiroaki Kumada]
- "*Design, Construction and Beam Commissioning of the 14 MeV Cyclotron for BNCT at CIAE*", Luyu Ji, China Institute of Atomic Energy
- "*Development of Neutron Production Targets for AB-BNCT*", Pedro Augusto Gaviola, National Atomic Energy Commission (CNEA)
- "*Neutron flux measurements in water phantom for BNCT*", Timofey Bykov, Budker Institute of Nuclear Physics

12:00-12:15 UTC - Break

12:15-13:30 UTC - **Talks 2&3, parallel sessions** (Room 1 and Room 2)
Room 1, Physics: Dosimetry I
[Chairs: Naonori Hu and Sara González]
-"*Measurement of the 14N(n,p) reaction at n_TOF – CERN: Implications in dosimetry of BNCT*", Pablo Torres-Sánchez, University of Granada
-"*Development of improved hybrid dose calculation algorithm using MC method and diffusion equation*", Mai Nojiri, Graduate School of Engineering, Kyoto University
-"*Microdosimetric analysis for Boron Neutron Capture Therapy through the Monte Carlo Track Structure simulation*", Yang Han, Nanjing University of Aeronautics and Astronautics & University of Pavia
-"*Detailed dosimetry of mixed fields using BNCT for skin cancer treatments*", Jessica Riback, National Atomic Energy Commission (CNEA)

-"*Monte Carlo simulations and in-vitro experiment to study if β-amyoid aggregates in Alzheimer's disease can be damaged by low energy neutron capture reactions*", Valeria Pascali, University of Pavia & National Institute of Nuclear Physics (INFN)

Room 2, Biology

[Chairs: María Pedrosa Rivera and Elena Delgrosso]

- "*A veterinary case report: beagle with mastadenoma and nasal carcinoma treated by twice BNCT*", Zhendong Lin, Neuboron Bioscience Ltd.
- "*Exploratory Study to Expand the Indication of Boron Neutron Capture Therapy Based on LAT1 Expression in Tumors*", Tsubasa watanabe, Institute for Integrated Radiation and Nuclear Science, Kyoto University
- "*Study of the biological response in-vitro to determine the validity of extrapolating the compound-dependent factor from glioblastoma to head and neck cancer in BNCT*", Patricia Álvarez Rodíguez, Biomedical Research Center (CIBM), University of Granada
- "*Evaluation of the effects of Boron Neutron Capture Therapy (BNCT) on proliferation of human keratinocytes in in-vitro epidermal models*", Stefania Ricci, University of Pavia

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DAY 2 - 15TH NOVEMBER - 10:00-14:00 UTC

10:00-10:30 UTC - **Educational Lecture 2, Biology** (Plenary room), "An updated overview of radiobiological studies using accelerator-based BNCT systems in the world"
Mitsuko Masutani, *National Cancer Center Research Institute, Tokyo, Japan*
[Chairs: Andrea Monti Hughes and Fong-In Chou]

10:30-10:45 UTC - Break

10:45-12:00 UTC - **Talks 1, Chemistry** (Room 1)
[Chairs: Taiki Morita and Takariho Nomoto]

- "*Carborane containing hydrindones as individual pharmacophores for BNCT: synthesis and chemical reactivity*", Salida Irbayeva, The Institute of Nuclear Physics of the Republic of Kazakhstan
- "*Development of Macrocyclic Polyamine-based Boron Delivery Agents for Neutron Capture Therapy*", Hiroki Ueda, Institute for Integrated Radiation and Nuclear Science, Kyoto University
- "*New Boron Analogues of Amino Acid-based Agents for Boron Neutron Capture Therapy*", Yinghuai Zhu, Sunshine Lake Pharma Co. Ltd.
- "*Selected 10-atom derivatives of mercaptoborate as substrates for the coupling reaction with the neurotransmitter protein", Karolina Wójciuk, National Centre for Nuclear Research*
-"Biocompatible Iron–Boron Nanoparticles Designed for Neutron Capture Therapy Guided by Magnetic Resonance Imaging", Vicenzo Amendola, University of Padova

12:00-12:15 UTC - Break

12:15-13:00 UTC - **Poster session A, Biology and Physics** (Poster Room)

13:00-14:00 UTC - **Talks 2&3, parallel sessions** (Room 1 and Room 2)
Room 1, Physics: Dosimetry II
[Chairs: Sol Espain and Stuart Green]
- "*Developments towards an adequate description of the dose-response relationship in the context of BNCT glioblastoma treatments*", Barbara Marcaccio, University of Pavia & National University of San Martín
- "*A photon isoeffective brain dose model for BNCT based on dose–response assessment from an animal model and its impact on a retrospective analysis of glioblastoma treatment.*", Ana Mailen Dattoli Viegas, National Atomic Energy Commission (CNEA)
- "*Study of intensity-modulated irradiation method for superficial tumors used accelerator-based BNCT*", Akinori Sasaki, Graduate School of Engineering, Kyoto University
- "*Study of the biological effects in glioblastoma cell lines after exposure to low and high LET radiation appearing in BNCT therapy*", Martyna Araszkiewicz, University of Warsaw & National Centre for Nuclear Research
Room 2, Imaging: Medical Images
[Chairs: Lucas Provenzano and Edyta Michaś-Majewska]
- "*A Versatile Treatment Planning System for basic research in BNCT*", Antònia Verdera, University of Granada
- "*A Self-Attention ResUnet to generate synthetic CT for MRI-guided BNCT* ", Sheng Zhao, Nanjing University of Aeronautics and Astronautics
- "*AI_MIGHT: Artificial Intelligence methods applied to medical images to enhance and personalize BNCT treatment planning*", Setareh Fatemi, National Institute of Nuclear Physics (INFN) Unit of Pavia
- "*Automatic segmentation of Head & Neck tumours in CT images using an nnUNet to enhance BNCT TPS*", Francesco Morosato, National Institute of Nuclear Physics (INFN) Unit of Pavia & University of Pavia

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DAY 3 - WEDNESDAY 16TH NOVEMBER - 10:00-14:00 UTC

10:00-10:30 UTC - **Educational Lecture 3, Physics** (Plenary room), "*The role and challenges of a Physicist in BNCT and What I learnt*"
Yuan Hao Liu, *Department of Nuclear Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing, China*
[Chairs: Silva Bortolussi and Hanna Koivunoro]

10:30-10:45 UTC - Break

10:45-12:00 UTC - **Talks 1, Imaging: Detectors** (Room 1)
[Chairs: Pablo Torres Sánchez and Hiroki Tanaka]
- "*Experimental Validation of a Spectroscopic and Imaging Detector Based on a LaBr3 Scintillator for Dose Monitoring in BNCT*", Anita Caracciolo, Politecnico di Milano
- "*Prompt gamma imaging for BNCT using a Compton camera*", Kiran Nutter, University of Birmingham
- "*Feasibility study of Prompt gamma-ray imaging by a Compton camera*", Makoro Sakai,

Gunma University
- "*Real-time Boron Concentration Monitoring Based on CdZnTe Compton Detector for the Accelerator-based Boron Neutron Capture Therapy: The First Experimental Study*", Changran Geng, Nanjing University of Aeronautics and Astronautics
-"*Capability of FBP, MLEM and OSEM to monitor boron dose using a Compton Camera in Boron Neutron Capture Therapy*", Chunhui Gong, Nanjing University of Science and Technology

12:00-12:15 UTC - Break

12:15-13:30 UTC - **Talks 2&3, parallel sessions** (Room 1 and Room 2)
Room 1, Physics: Neutron Detectors
[Chairs: Setareh Fatemi and Nikolaos Voulgaris]
- "*Silicon carbide detectors for BNCT*", Aixeen Fontanilla, Frascati National Laboratory of National Institute of Nuclear Physics (INFN-LNF)
- "*The BNCT neutron spectrometer NCT-WES: the NPL experimental validation campaign*", Alessandro Calamida, Frascati National Laboratory of National Institute of Nuclear Physics (INFN-LNF)
- "*Development of a compact multi-elements activation neutron spectrometer for BNCT*", Ettore Mafucci, University of Torino
- "*Validation of A Spectrometer To Measure Epi-thermal Neutrons Using A Position Sensitive Proportional Counter - Development of pencil-beam epi-thermal neutron source with a DT neutron source* ", Yu Fujiwara, Osaka University
- "*Measuring the near-target neutron field of a D–D fusion facility with the novel NCT-WES spectrometer*", Abner Iván Castro-Campoy, Frascati National Laboratory of National Institute of Nuclear Physics (INFN-LNF)
Room 2, Biology 2
[Chairs: Hiroyuki Nakamura and Patricia Alvarez]
- "*Efficacy of integrin targeting novel boron carrier for boron neutron capture therapy in F98 rat glioma bearing brain tumor models*", Kohei Tsujino, Osaka Medical and Pharmaceutical University
- "*Novel precision BNCT strategy using a new boron agent targeting high-grade pancreatic cancer*", Takya Fujimoto, Neutron Therapy Research Center, Okayama University
- "*Breast cancer cells sensitization by gold nanoparticles in the case of Boron-Neutron Capture Therapy - the impact on cell cycle distribution and gamma-H2AX foci formation*", Wiktoria Krakowiak, Jan Kochanowski University in Kielce
- "*Lithium neutron capture therapy as a potential melanoma treatment modality*", Anna Kasatova, Budker Institute of Nuclear Physics

13:30-14:00 UTC - Social activity (Social Room and Lobby)
[Host: Naonori Hu and Ian Postuma]

DAY 4 - 17TH NOVEMBER - 10:00-14:00 UTC

10:00-10:30 UTC - **Educational Lecture 4, Chemistry** (Plenary room), "*Drug delivery systems for boron neutron capture therapy*"
Takahiro Nomoto, *Tokyo Institute of Technology, Tokyo, Japan*
[Chairs: Taiki Morita and Po Shen Pan]

10:30-10:45 UTC - Break

10:45-11:45 UTC - **Talks 1, Biology III** (Room 1)
[Chairs: Natsuko Kondo and Anna Kasatova]
-"*BORON BIODISTRIBUTION STUDY FOR BNCT WITH BORIC ACID AND BORONOPHENYLALANINE IN AN ORAL CANCER MODEL*", Paula Sofía Ramos, National Atomic Energy Commission (CNEA)
- "*Oligo-Fucoidan enhances BPA-BNCT therapeutic effect on tumors: studies of boron biodistribution/microdistribution and microbiota in the hamster cheek pouch oral cancer model*", Andrea Monti Hughes, National Scientific and Technical Research Council (CONICET) & National Atomic Energy Commission (CNEA)
- "*Therapeutic efficacy and radiotoxicity of BNCT employing Oligo-Fucoidan and Glutamine as adjuvants in an experimental model.*", Debora N Frydryk Benitez, National Atomic Energy Commission (CNEA)
- "*Bystander effect and immune genes expression in HT29 colon adenocarcinoma cell line with Boron Neutron Capture Therapy.*", Yanina Ferreyra, National Atomic Energy Commission (CNEA)

11:45-12:15 UTC - Break

12:15-13:00 UTC - **Poster session B, Chemistry + Imaging + Clinics + Physics** (Poster Room)

13:00-14:00 UTC - **Talks 2&3, parallel sessions** (Room 1 and Room 2)
Room 1, Physics: Radioprotection & Gamma Detectors
[Chairs: Valeria Mont and Evgeniia Sokolova]
- "*Radioprotection assessment of an AB-BNCT Lab*", María Eugenia Capoulat, National Atomic Energy Commission (CNEA)
- "*Radiation safety consideration, design, and commissioning of the Xiamen Humanity Hospital-Neuboron BNCT Center*", Caifeng Meng, Neuboron Therapy System Ltd.
- "*The gamma-ray dose evaluation with optically stimulated luminescent dosimeter of BeO in BNCT*", Nishiki Matsubayashi, Graduate School of Engineering, Kyoto University
- "*Development of Real-time Gamma-ray Spectrum / Dose Monitor -Investigation of true real-time convergence-*", Nikolaos Voulgaris, Osaka University
Room 2, Imaging: Autoradiography
[Chairs: Ian Postuma and Barbara Marcaccio]
- "*Machine learning based image classification in neutron autoradiography*", Julia Sabrina Viglietti, National Atomic Energy Commission (CNEA)
- "*Optical density analysis in autoradiographic images for the study of preferential boron uptake in broncho-vascular tree and its effects on lung dosimetry*", María Sol Espain,

National Scientific and Technical Research Council (CONICET) & National Atomic Energy Commission (CNEA)
- ”*Development of indirect neutron radiography for BNCT beam characterization at Xiamen Humanity Hospital-Neuboron BNCT Center*”, Xinyu Wang, Nanjing University of Aeronautics and Astronautics
- “*Fundamental Study on T/N Ratio Determination by Ex-vivo Macro-imaging of BPA with A brain tumor model rat for BNCT*”, Yugo Tokumaru, Osaka university

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DAY 5 - 18TH NOVEMBER - 10:00-14:00 UTC

10:00-10:30 UTC - **Educational Lecture 5, Clinics** (Plenary room), "BNCT for malignant brain tumors, reactor to accelerator"
Shin-Ichi Miyatake, *Kansai Medical BNCT Center, Osaka Medical and Pharmaceutical University, Japan*
[Chairs: Woo Kim and Minoru Suzuki]

10:30-10:45 UTC - Break

10:45-11:45 UTC - **Talks 1, Clinics** (Room 1)
[Chairs: Woo Kim and Minoru Suzuki]
- “*A Flexible Patient Position Method Combined with Treatment Planning System NeuMANTA for BNCT*”, Jiang Chen, Neuboron Therapy System Ltd.
- “*Promoting the use of a common language for specifying and reporting the doses in Boron Neutron Capture Therapy*”, Yi-Chiao Teng, Neuboron Therapy System Ltd.
- “*Interim results of accelerator based BNCT RCT for refractory high-grade meningiomas*”, Shin-Ichi Miyatake, Kansai BNCT Medical Center & Osaka Medical and Pharmaceutical University
- “*Should Canada Join the Preclinical and Clinical Research of Boron Neutron Capture Therapy?*”, Ming Pan, Windsor Regional Hospital Cancer Program

11:45-12:15 UTC - Social activity (Social Room)
[Host: Setareh Fatemi]

12:15-12:30 UTC - Break

12:30-13:30 UTC - **Closure** (Plenary room): Awards announcement, next meeting presentation and Closure.

ABSTRACT BOOK

Contents

Detectors

ID:4 - Experimental Validation of a Spectroscopic and Imaging Detector Based on a LaBr3 Scintillator for Dose Monitoring in BNCT

Anita Caracciolo[1,2], Davide Di Vita[1,2], Tommaso Ferri[1], Marco Carminati[1,2], Nicoletta Protti[3,4], Saverio Altieri[3,4], Franco Camera[2,5], Carlo Fiorini[1,2]

1 Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano, 20133, Italy

2 Istituto di Fisica Nucleare (INFN), Sezione di Milano, Milano, 20133, Italy

3 Dipartimento di Fisica, Università di Pavia, Pavia, 27100, Italy

4 Istituto di Fisica Nucleare (INFN), Sezione di Pavia, 27100, Italy

5 Dipartimento di Fisica, Università degli Studi di Milano Statale, Milano, 20133, Italy

In this work we present the experimental validation of a gamma ray detection prototype, based on a 2" cylindrical LaBr3(Ce+Sr) scintillator crystal, read by a matrix of 64 Silicon Photomultipliers (SiPMs), as a basic element for a SPECT system for dose monitoring in Boron Neutron Capture Therapy (BNCT). The goal of the system is to detect the 478 keV gamma rays emitted by the excited 7Li produced in 94% of the boron neutron capture reactions, to have a real-time quantification and localization of the local dose released to the patient [1, 2]. However, the detection of these gamma rays is very challenging because of the high intensity neutron source required in BNCT, that leads to a severe background of neutrons and secondary gamma rays. In order to validate the spectroscopic capabilities of the detector, 10B-loaded samples have been irradiated inside the Prompt Gamma Neutron Activation Analysis (PGNNA) facility of TRIGA Mark II (Pavia, Italy) [3], with thermal neutron fluxes of the order of 10^5 n/cm^2/s. The good energy resolution of the detector (2.7% FWHM at 662 keV [4]) has allowed to resolve in each acquired spectrum the BNCT photopeak at 478 keV from the adjacent photopeak at 511 keV, generated by pairs production of high energy gamma rays. Therefore, it has been possible to calculate the number of events under the peak, after background subtraction and gaussian fit with Matlab. The number of detected events at 478 keV has been found to increase linearly with the boron concentration of the vials irradiated (0 ppm, 62 ppm, 125 ppm, 250 ppm, 500 ppm, 1000 ppm). During these measurements cadmium foils around the detector have been used to lower as much as possible the neutron activation of both the electronics boards and the scintillator crystal, but, in view of its possible application in a real BNCT scenario, where a neutron flux of 10^9 n/cm^2/s is required, the development of a dedicated shielding case is necessary. Moreover, to allow imaging capabilities of the prototype, the design of an appropriate collimator is under development. A preliminar position sensitivity of the detector has been verified by substituting the cylindrical 2 inches crystal with a square one, with dimensions 5cmx5cmx2cm. The 2-D position reconstruction has been carried out by irradiating the module in 256 points with a 1 mm 137Cs collimated source (662 keV), and a distance of 3.12 mm between the points. XY coordinates reconstruction is a supervised learning problem since the irradiated spots are known a priori. The SiPMs signals patterns acquired in each different irradiation position have been used to train a Convolutional Neural Network (CNN), that has two branches for the prediction of the x and y interaction position coordinates. The accuracy of the CNN has been found to be about 65% for both the reconstruction of the x and y and 90% if including also the adjacent pixels. The measurements show also a spatial resolution of the reconstructed position of 3.6 mm.

References 1. Kobayashi, T., et al. "A noninvasive dose estimation system for clinical BNCT based on PG-SPECT—Conceptual study and fundamental experiments using HPGe and CdTe semiconductor detectors." Medical physics 27.9 (2000): 2124-2132. 2. Valda, A., et al. "Development of a tomographic system for online dose measurements in BNCT (Boron Neutron Capture Therapy)." Brazilian journal

of physics 35.3B (2005): 785-788. 3. Giuntini, L., et al. "Detectors and cultural heritage: The INFN-CHNet experience." Applied Sciences 11.8 (2021): 3462. 4. Caracciolo, A., et al., "BeNEdiCTE (Boron Neutron CapTurE): a Versatile Gamma-Ray Detection Module for Boron Neutron Capture Therapy." IEEE Transactions on Radiation and Plasma Medical Sciences (2022).
corresponding author email: anita.caracciolo@polimi.it

ID:7 - Design Study of Real-time Absolute Epi-thermal Neutron Flux Intensity Monitor using Scintillation Detectors

Jiye Qiu[1], Daisuke Hatano[1], Shingo Tamaki[1], Sachie Kusaka[1], Isao Murata[1]

1 Division of Sustainable Energy and Environmental Engineering, Graduate School of Engineering, Osaka University

In BNCT, epi-thermal neutron irradiation is carried out to treat deep-seated cancers, as epi-thermal neutrons can be slowed down in a human body and converted into thermal neutrons before reaching the tumor. Since the number of irradiated epi-thermal neutrons determines the therapeutic effect, it is significantly required to measure the absolute epi-thermal neutron intensity during the irradiation. Thus, we have been developing a novel monitor to measure the absolute epi-thermal neutron flux intensity on the body surface of a patient in real-time during BNCT treatment.

The objective of this study is to design a monitor that has a flat response to epi-thermal neutrons in the range of 0.5eV to 10keV, and has no sensitivity outside the epi-thermal neutron energy region. We employed two potential neutron detection elements which are 6Li and 10B containing scintillators, i.e., LiCAF crystal scintillator based on 6Li(n, α)3H reaction, and EJ-254 plastic scintillator based on 10B(n, α)7Li reaction. We used PHITS code to calculate the epi-thermal neutron response of these two scintillators when absorbers with various thicknesses are covered. Based on the simulation results, we designed monitors by combining the responses of three scintillation detectors covered by boron absorbers with different thicknesses for both LiCAF and EJ-254 scintillators. As a result, we successfully minimized the response to the thermal and fast neutron energy regions, and made a flat response in the epi-thermal neutron energy region. Now we are planning to carry out experiments to evaluate the performance of the two scintillators, LiCAF and EJ-254, so as finally to validate their designs.
corresponding author email: jiyeqiu22@qr.see.eng.osaka-u.ac.jp

ID:12 - Development of Real-time Gamma-ray Spectrum / Dose Monitor -Investigation of true real-time convergence-

Nikolaos Voulgaris[1], Takaaki Miyoshi[1], Tamaki Shingo[1], Sachie Kusaka[1], Isao Murata[1]

1 Osaka University

In order to raise awareness of radiation exposure and reduce the amount of radiation exposed to the medical staffs who work in clinical radiation environments, our research group is developing a portable monitor that can measure the energy spectrum and dose of gamma-rays simultaneously in real time. In this monitor, the pulse height distribution of gamma-rays is measured, converted to energy spectrum, and the dose is derived in turn by applying a dose conversion coefficient to the energy spectrum. The monitor consists of a CsI (Tl) crystal and a multi-pixel photon counter (MPPC). In previous research by our group, in order to measure the energy spectrum in real time, we employed an improved sequential Bayesian estimation method (k-αmethod). Experimental verification of this monitor has been carried out not only with standard gamma-ray sources, but also in the background field (0.08 Sv/h) as well as the nuclear fuel storage room of the author's laboratory (2 Sv/h) in order to evaluate the practicality of the monitor in a field with a complex energy spectrum. If the radiation counting rate is sufficiently high at about 1000 cps, the energy spectrum can be estimated in about 30 seconds and the dose can be estimated immediately, and even in a low background field of 46 cps, the dose can be estimated in 30 seconds. The Bayesian estimation method is a method of probabilistically inferring the cause of an event from a newly obtained observed event, and it is possible to estimate the cause event with higher accuracy by revising continuously by the newly obtained observed event. However, convergence criteria and error propagation have not been resolved in actual measurements with statistical errors. Until now the convergence of the energy spectrum was determined visually from the time dependent change of the spectrum and dose. Thus, a more quantitative procedure for determining the convergence was deemed necessary. In our research, an evaluation of criteria for the convergence of the energy spectrum and number of counts

was therefore carried out. To carry out the evaluation, the residual NAE (Normalized Absolute Error) between the estimated pulse height distribution derived by multiplying the estimated energy spectrum by the response function R and the true pulse height distribution obtained from the measurements, was defined. The absolute value of NAE depends on the nuclide used, as well as the environment, but the NAE converges to a constant value for each nuclide and environment. By investigating the energy spectra, though inductive, it was found that they all converged at the same degree of revision, that is number of counts. In the previous studies, to simulate a real-time measurement our research group once measured a pulse height distribution over a certain time period and the measurement simulation was carried out by pseudo-obtaining a signal by resampling from the measured pulse height distribution at each count. This process has an advantage that the measurement has reproducibility, but it does not actually perform true real-time estimations. Therefore, in our research, in order to perform true real-time estimations, we introduced a measuring instrument (DP5, Amptek, Inc.) that has a capability of obtaining a detected pulse height and time stamp data as a set. And the obtained pulse height and time stamp data are processed by the k- αmethod continuously in real-time. The obtained results were compared with the results estimated by the previous resampling method. From the comparison it was shown that the true real-time and resampling estimates agreed, demonstrating that it is possible to estimate the energy spectrum and dose in true real-time.

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ID:19 - Validation of A Spectrometer To Measure Epi-thermal Neutrons Using A Position Sensitive Proportional Counter - Development of pencil-beam epi-thermal neutron source with a DT neutron source -

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We have been developing a new spectrometer to measure energy spectra especially in the epi-thermal neutron region for BNCT. In recent years, BNCT with Accelerator-Based Neutron Source (ABNS-BNCT) has been available, and thus the characterization of the neutron fields generated by the accelerators has become a more important issue. The present neutron spectrometer is based on a position-sensitive ^{3}He proportional counter. In the author's group, a novel technique was developed to estimate the neutron spectrum from detection position information in the ^{3}He counter. The neutron spectrum estimation is carried out by Bayesian estimation process. Currently, the validation of the spectrometer is underway. For this we developed an epi-thermal neutron source, and tried to apply to validation of the spectrometer. However, it was found that neutrons incident from the side surface of the detector have a significant impact on the accuracy of the validation measurement. Then, to cope with this problem, we designed and constructed a new Beam Shaping Assembly (BSA) with a pre-collimator to suppress the effect of neutrons incident from the side surface. Assuming a DT neutron source, we focused in particular on the design of "pre-collimator" that collimate the neutron flow to prevent its side incidence to the spectrometer. The design calculations were carried out by MCNP5. We now completed the design, i.e., determination of its materials and dimensions through the following four determination processes: (1) material, (2) horizontal length of the pre-collimator, (3) aperture of the pre-collimator, and (4) distance between the pre-collimator and the epi-thermal neutron column, taking the design goals listed below into account: I. Percentage of the number of neutrons penetrating the detector from the front surface to the end surface to that of neutrons counted by the detector is 99% or more. II. Number of neutron counts by the spectrometer is 10 or more for 5 hours. As the result of the design, four parameters of the pre-collimator were successfully determined as in the following: (1) Polyethylene as the material, (2) 70 cm as the horizontal length, (3) 1.6 cm as the aperture diameter, and (4) 300 cm as the distance between the pre-collimator and the epi-thermal neutron column.

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ID:24 - The gamma-ray dose evaluation with optically stimulated luminescent dosimeter of BeO in BNCT

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The irradiation fields in BNCT have neutrons with wide energy range and undesired high intensity -rays. For quality assurance (QA) of the treatment, the -ray doses in water phantom were measured before each treatment. Since the thermo-luminescent dosimeter (TLD) of BeO powder enclosed in a quartz glass capsule (Panasonic, UD-170LS) that have been used for BNCT dosimetry is out of production, a new type of -ray dosimeter is needed. In this study, we selected optically stimulated luminescent dosimeter (OSLD), which is made of BeO ceramic and investigated whether the OSLD can be used in the field of BNCT. We used myOSLchip dosimeters (Freiberg Instruments, Germany). The size of the BeO element was 4.65×4.65×0.5 mm and the elements were held in the sheath made Acylnitril-Butadien-Styrol-Copolymere (ABS). The OSLDs were irradiated in free-air and surrounded with polytetrafluoroethylene (PTFE) plates of 5 mm thickness to ensure build-up. To determine the relation between the OSL signal and the -ray dose value, the calibration test was performed at Co -ray source in Institute for Integrated Radiation and Nuclear Science, Kyoto University (KURNS). The -ray dose rate was measured by an ionization chamber and the OSLDs were irradiated at 150, 300, 450 mGy by changing the irradiation time. The irradiation tests of BNCT irradiation field were performed at the Heavy Water Neutron Irradiation Facility (HWNIF) at Kyoto University Research Reactor in KURNS. The Cd shutter of 1 mm thickness was installed to change the thermal neutron flux with each aperture. To investigate the sensitivity to thermal neutrons, the irradiation tests were carried out by changing the Cd shutter aperture to 200, 300, and 600 mm. We tested the performance of the dosimeters and measured the influence of thermal neutron on the -ray dose obtained by the OSLD. The OSLDs had a good -ray dose linearity of around 500 mGy corresponding to the dose in QA procedure of BNCT, and the thermal neutron sensitivity of the OSLD was less than that of TLD.
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ID:42 - Silicon carbide detectors for BNCT

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Within the INFN ENTER-BNCT project, a single moderator directional neutron spectrometer called NCT-WES (Neutron Capture Therapy Wide Energy Spectrometer) was successfully developed as a real-time neutron beam monitor for BNCT clinical applications. This device condenses the performance of the conventional Bonner spheres into one cylindrical moderator embedding six semiconductor-based thermal neutron detectors. Silicon detectors were originally employed, but their limited radiation resistance makes them unsuited for routine clinical use. Thus, commercially available silicon carbide detectors with 1 mm2 sensitive area were studied for this purpose. Two different thermal neutron radiators were exploited, leading to different measurement sensitivities and degrees of radiation resistance: (1) a 6LiF coating on the sensor or (2) the air volume between the sensor surface and the walls of the package. Thermal neutron sensitivity and radiation resistance were tested in the well-controlled thermal neutron beam produced in the thermal column of the TRIGA reactor at LENA Pavia. The sensors were connected to a nuclear spectroscopy system and irradiated to an accumulated fluence of 5.6×1013 cm-2 distributed in nine steps, ranging from 1012 cm-2 to 1013 cm-2 each, with the reactor operating at the maximum

power of 250 kW. After every ”damaging step” the reactor power was lowered to 100 W and the pulse height distribution of the detectors was recorded. This allowed observing the effects of the progressive damage in the pulse height distribution. These effects were evident in the 6LiF coated detector, and fairly observable in the air-type detector. To interpret the spectra, a specific Monte Carlo code was written to model the neutron interaction in both detectors, achieving very satisfactory agreement with the experiment.
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ID:46 - Experimental verification of real-time -ray energy spectrum and dose monitor up to 3 MeV.

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Radiation has become indispensable in modern medicine. However, in the medical field, although the treatment of patients tends to be prioritized, the radiation exposure of medical personnel tends not to be so emphasized. In this research, we are developing a portable spectrometer that can simultaneously measure the energy spectrum and dose of rays in real time for medical practice. We believe that this measuring instrument will have the effect of changing awareness of medical professionals themselves about radiation exposure and finally reducing their exposure in the medical field. The authors' group has developed a prototype spectrometer and confirmed the basic characteristics using standard -ray sources. In addition, measurements in the nuclear fuel storage room, where a large number of -rays are present, have shown that spectral reconstruction and dose estimation can be carried out simultaneously in real time in stronger radiation conditions compared to background circumstances. The spectrometer utilizes a CsI (Tl) crystal (2.6 x 2.6 x 2.6 cm3) and a scintillation detector with a Multi-Pixel Photon Counter (MPPC), with the advantages of small size and light weight. The spectrometer measures a pulse height spectrum of gamma rays. The pulse height spectrum is converted into an energy spectrum by the unfolding process with the detector response function R, and the dose is calculated by multiplying a dose conversion coefficient to this energy spectrum. In order to realize real-time measurement of the energy spectrum, the sequential Bayesian estimation method is used to convert the pulse height distribution obtained from the measurement into an energy spectrum.

In this study, we confirm experimentally whether the measurement range of the prototype -ray detector can be extended to 3 MeV, the maximum energy of -rays remaining after radiotherapy. For this purpose, an Al foil was irradiated with DT neutrons to induce 27Al(n,α)24Na reaction, which produces radioactive 24Na, emitting -rays of 2.75 MeV. The gamma-rays were then measured by the present monitor, and the results were compared with the theoretical values to finally validate the present monitor.
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ID:73 - Design of BNCT-SPECT by PHITS - Aiming at high-precision measurement by analyzing crosstalk phenomena -

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Currently, it is not possible to determine the treatment effect of boron neutron capture therapy (BNCT) in real time. In order to solve this problem, we are developing a new SPECT system (BNCT-SPECT) to obtain 3D images of the treatment effect of BNCT, which is based on the principle of measuring 478 keV -rays immediately emitted from the excited state of 7Li produced by the 10B(n,α)7Li reaction. In the previous study, the basic design study of a BNCT-SPECT system with a GAGG(Ce) scintillator was performed by using MCNP assuming a single detection element. [1] However, it was found to be difficult to measure the treatment effect with a high accuracy due to a large amount of background noises in the measured data in BNCT treatment field, since the result showed 0.231 of S/N ratio and 5.45 % of statistical accuracy, and the performance goals of the present instrument were not achieved, which were originally set as the signal-to-noise ratio more than 1.0 and statistical accuracy less than 2%. To improve these performances, we are considering to utilize noise signals made by the crosstalk phenomena, that are detected simultaneously by multiple detectors. However, because MCNP cannot

treat coincidence event directly, we considered to conduct design study of BNCT-SPECT by the radiation transport code PHITS, which is capable of coincidence analysis, to investigate the feasibility of this idea and evaluate the performance of the designed system. In this study, we evaluated the performance of a BNCT-SPECT system with a single detection element calculated by PHITS to confirm the validity of this code for the basic design study of BNCT-SPECT, by comparing the simulation result with that of calculated by MCNP, which was employed in the previous study. At first, actual treatment site of BNCT was simulated and the measured pulse height spectrum by BNCT-SPECT system was calculated. Pulse height spectrum was separately analyzed into the following four types : (1) 478 keV -rays by 10B(n,α)7Li reaction, which indicate the treatment effect, (2) 155Gd and 157Gd capture -rays emitted in the GAGG(Ce) scintillator, (3) induced -rays produced by incident neutrons in the GAGG(Ce) scintillator, and (4) other -rays excluding (1), (2), and (3), such as 2.22 MeV capture -rays emitted from 1H(n,)2H reaction in the human body, 511 keV annihilation -rays , and so on. After that, we evaluated the noise levels caused by (2) to (4) in the peak energy band of 478 keV -rays, which indicates the treatment effect. Finally, we derived the signal-to-noise ratio and statistical accuracy, which indicates the performance of the system. As a result, the signal-to- ratio of 478 keV -rays, i.e., the ratio of the signal of (1) to the noise signals, (2) to (4), was 0.230, and the statistical accuracy was 5.50 %, and these results mostly agreed with the calculated results by MCNP in the previous study. In conclusion, hence the results of the performance evaluation by PHITS was successfully reproduced the basic design of BNCT-SPECT by MCNP, PHITS was found to be available for the design study of BNCT-SPECT. In future, we will investigate the feasibility of improving the performance of BNCT-SPECT by PHITS considering the coincidence and anti-coincidence of multiple detectors, practically the background noise can be reduced by utilizing the crosstalk phenomena for designing the final BNCT-SPECT system.

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ID:95 - Development of indirect neutron radiography for BNCT beam characterization at Xiamen Humanity Hospital-Neuboron BNCT Center

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Background and purpose of the study: Once a BNCT center is built, one of the most important things is the characterization of its neutron beam, which is critical to its beam design verification and clinical validation. Xiamen Humanity Hospital-Neuboron BNCT Center (XHH BNCT Center) has completed the construction and system installation in 2021, and is currently conducting beam characterization measurements and preclinical animal experiments. During this period, our group developed a measurement platform and method for indirect neutron radiography and successfully realized the neutron flux distribution measurement over the cross section of epithermal neutron beam. Materials and Method: The measurement platform for neutron autoradiography include imaging plate, reader device, metal plate, and exposure frame, etc. The imaging plate (ST-VI, 14×17 inch) and its reader device (CR-IR 357) are from Fuji’s CR system. Two types of metal plates, copper and aluminum, are used to be activated by neutron beam. A frame made of aluminum was built for the exposure of activated metals, using which the influence of scattered rays from decaying particles on the measurements could be minimized. Based on this platform, the fading and temperature-dependent characteristics of imaging plate were first studied using radioactive sources, and the relationship between the dose deposition of decaying particles received by the imaging plate and the photostimulated luminescence (PSL) intensity was also investigated. The above results are used for the calibration and correction of the measured radioactivity of metal plate, thus achieving more accurate measurement of neutron flux distribution. For the neutron flux distribution measurement, the copper plate was irradiated for 12 min with epithermal neutron beam to perform the indirect neutron radiography. And then it was exposed to the imaging plate for 30 min. Regarding the use of aluminum plate, it was irradiated for 22.5 min (10 half-lives of Al-28), and its exposure time was set as 20 minutes. Results: Results show that the PSL intensity decreases with the increasing time from

the end of exposure, and the fading of PSL intensity is temperature dependent. A fitting formula was established to correct the fading in imaging plate. Meanwhile, the response curve of PSL intensity to dose deposition was obtained, which can be used for the reaction rate determination of metal plate. Finally, the neutron flux distribution of epithermal neutron beam at XHH BNCT Center was measured by using indirect neutron autoradiography. Conclusions: Combining the fading correction of PSL intensity and the its relationship with dose deposition of decay particle, a method of indirect neutron radiography was established at XHH BNCT Center, and the neutron flux distribution of epithermal neutron beam was successfully obtained.

Keywords: BNCT; Indirect neutron autoradiography; Imaging plate; PSL.
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Physics

ID:5 - Study of impurity accumulation in a lithium neutron-generating target

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An accelerator based epithermal neutron source for the development of boron neutron capture therapy (BNCT), a promising method for the treatment of malignant tumors, is proposed, created and is functioning at the Budker Institute of Nuclear Physics. The neutron source consists of a tandem accelerator of charged particles of an original design, a lithium neutron-generating target, for generating neutrons as a result of the ^{7}Li(p,n)^{7}Be reaction, and a beam shaping assembly for forming a therapeutic beam of epithermal neutrons. The purity of the lithium layer affects the yield of neutrons from the target, which makes it important to determine the elemental composition of the target. Lithium is known to actively interact with air. The compounds formed during this interaction reduce the neutron yield from the lithium neutron-generating target. In this work, the accumulation of impurities in a lithium target as a function of exposure to air and the proton fluence on the target, was investigated by energy analysis of backscattered protons. The spectrum of backscattered protons was measured with a semiconductor silicon detector (Si Charged Particle Radiation Detectors for Alpha Spectroscopy). The results obtained are extremely important for the prolonged generation of a stable neutron flux for boron neutron capture therapy and other applications. This research was funded by Russian Science Foundation, grant number 19-72-30005.

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ID:6 - Neutron flux measurements in water phantom for BNCT

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A compact accelerator-based neutron source has been developed at the Budker Institute of Nuclear Physics in Novosibirsk, Russia [1]. The lithium target installed in the BSH is used to generate neutrons. A water phantom is used to measure the neutron flux. The water phantom is a volume, with a movable carriage, which is driven by two stepper motors. Neutron flux is measured with a fast neutron sensor [2] with Boron-10 mounted on a movable carriage. Software was developed that allows automatic measurements of the neutron flux in the entire volume of the phantom. This paper describes the software of the phantom and the process of measurements. Acknowledgments: This research was funded by a grant from Novosibirsk State University “Software for the neutron research” within the framework of the project X-ray, synchrotron, neutron methods of interdisciplinary research.

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ID:22 - Microdosimetric analysis for Boron Neutron Capture Therapy through the Monte Carlo Track Structure simulation

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Background: Boron Neutron Capture Therapy (BNCT) is a cellular-level hadron therapy that achieves therapeutic effects through the synergistic action of multiple particles including lithium, alpha, proton, and photon, making the relative biological effect (RBE) of BCNT still a challenge to evaluate. Microdosimetry analysis is an option to solve this problem through statistical analysis of the lineal energy or specific energy in a micro- and nano-sensitive volume representing the different biological targets. Particle transport simulation with low-energy particles makes it possible to analyze the specific microdosimetric characteristic with heterogeneous boron distribution at the subcellular scale. The conventional Monte Carlo transport method is based on condensed history algorithms, which may not be usable with the small sensitive volume and wide step-size range. Geant4-DNA is a Monte Carlo Track Structure simulation software, enabling a more reliable simulation of low-energy particle transport. However, the Geant4-DNA performs rough handling of the ionization transport for ions with the energy lower than 0.5 MeV/u in "G4EmDNAphysics" because of the charge exchange process, making it a challenge to complete the step-by-step simulation of lithium in BNCT. In this work, a BCNT microdosimetry study was performed by the Monte Carlo Track Structure simulation software, TOPAS-nBio, built on the framework of Geant4-DNA, with an amended cross-section of lithium. Methods: For the customer-adjustable physics model, "TsEmDNAphysics", we used a modified ionization cross-section of lithium, labeled as "rudd_li", which was obtained through the effective charge cross-section scalation method and phenomenological double-parameter modification. For other particles, "TsEmDNAphysics" executes the same physics models with G4EmDNAphysics_option2. We verified the range and stopping power of lithium, alpha, and proton with corresponding energies in BNCT. Besides, the lineal energy spectra of four different particles (lithium, alpha, monoenergetic protons, recoil protons) and two different boron heterogeneity distributions (BPA, BSH) were calculated using a geometric model including 27 cells. The lineal spectra were analyzed and compared with the results of the TEPC experiment and Phits simulation. Results: The excellent agreement of range and stopping power through simulation and ICRU 73/90 indicates that TsEmDNAphysics with the revised lithium cross-section can well accomplish the track structure simulation of low-energy charged particles in the BNCT environment. The frequency-mean lineal energies of the monoenergetic proton, recoil proton, boron BPA, and boron BSH are 15.6782, 13.4146, 53.1661, and 57.3164 keV/ m, respectively, and the dose-mean lineal energies are 50.7649, 46.0959, 162.6315, and 133.7825 keV/ m. The spatial distribution of boron has a significant effect on the lineal energy spectra for lithium but not for alpha. The results for monoenergetic protons and recoil protons have similar lineal energy distributions. Conclusion: The Monte Carlo Track Structure simulation platform for BNCT microdosimetric analysis has been established, which could be used for biological dose correction in the treatment planning system, source evaluation, and new boron drug development. Subsequently, we will use the current platform to analyze the biological effects of BNCT at the DNA damage scale.

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ID:32 - Study of intensity-modulated irradiation method for superficial tumors used accelerator-based BNCT

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To adapt accelerator-based BNCT to superficial tumors, we revealed that a uniform thermal neutron flux distribution can be formed using a bolus for tumors with a diameter of about 50 mm. When a superficial tumor of about 10 cm in diameter spreads over a wide area, we proposed an intensity-modulated irradiation method. An intensity modulator is installed in a collimator aperture to intentionally form a non-uniform dose distribution, and multiple irradiation fields are overlapped to irradiate the tumor with uniform thermal neutron flux to improve the dose distribution. In this study, we developed a method to automatically determine the optimal combination of intensity modulators using the SERA. The dose distribution of angiosarcoma treated by intensity-modulated irradiation using this method was evaluated. SERA was used for dose evaluation. CT images were selected from the Cancer Imaging Archive. A Neucure® of the Kansai BNCT Medical Center was used as the neutron source, and the diameter of the collimator was set to 15 cm. The maximum number of irradiated field combinations was two. The treatment for the angiosarcoma of 10 cm in diameter and 1 cm in thickness located on the top of the head was assumed. The limiting doses for the skin or brain were 12 or 15 Gy-eq, respectively. The intensity modulator installed in a collimator aperture as irradiation field 1 was a polyethylene (PE) disk of 15 cm in diameter, and 2 cm in thickness. A 6 cm x 6 cm hole was formed in the center of a PE disk as irradiation field 2. The hole was filled with PE loaded with lithium fluoride (LiF-PE) blocks with the size of 1 cm x 1 cm and 2, 3, 4, or 5 cm thickness, and the unfilled areas were made into 2 cm thick PE. The number of patterns of the LiF-PE shape was set to 424 to search for the contribution to the improvement of dose distribution. The best one with the lowest tumor dose was selected as the optimal solution for irradiation field 2 when irradiated with irradiation time ratios of 1:2, 1:3, 1:4, and 1:5 for irradiation field 1 and field 2, respectively. The advantage of the intensity-modulated irradiation method was verified by comparing the minimum tumor dose with treatment in irradiation field 1 only. The minimum tumor dose was 21 Gy-eq when treatment was performed in irradiation field 1 only. On the other hand, the minimum tumor dose was 25.9 Gy-eq in intensity-modulated irradiation. In addition, the uniformity of dose distribution was improved by 36%. We developed a method to automatically determine the optimal combination of intensity modulator and irradiation time ratio to perform intensity-modulated irradiation for superficial tumors using SERA. We were able to demonstrate the effectiveness of the accelerator-based BNCT for intensity-modulated irradiation of superficial tumors. In the future, we will improve the algorithm for determining the intensity modulator and time ratio in this method, search for more applicable cases, and evaluate the results by actual measurements.

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ID:40 - Cold neutron producing in the compact accelerator-based neutron source

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The compact accelerator-based neutron source at the Budker Institute of Nuclear Physics generates neutrons of a wide energy range: epithermal neutrons used for research in the boron neutron capture therapy (BNCT), thermal neutrons for measuring the activation spectrum, and fast neutrons for radiation testing of new materials. Neutrons with energies in the range of 10^{-7}-5 10^{-3} eV have distinct wave properties and can be regarded as neutron waves. Such properties of neutrons open up new possibilities for research in the field of BNCT and neutron diffractometry. In this work, the first steps were taken to produce cold neutrons at the compact accelerator-based neutron source. For this purpose, a series of experiments aimed at testing several models of neutron moderators were conducted. Principle scheme of the experiment: on the compact accelerator-based neutron source during threshold reaction ^{7}Li(p,n)^{7}Be a neutron flux with intensity $2 \cdot 10^{12}$ and average energy 50 keV is generated when a proton beam with energy up to 2.1 MeV hits a lithium target. Then epithermal neutron flux is directed to the tested moderator. A multilevel deceleration system consisting of heavy and ordinary water at room temperature and 73 K was tested as a moderator. After passing through it, the neutrons are detected by a detection system consisting of a GS-20 neutron detector with a lithium-containing scintillator (The Saint-Gobain Crystals, USA) and plastic boron-enriched polystyrene scintillators (IHEP, Protvino). Neutrons with energies less than 10^{-3} eV were obtained and the dependence of their number on the thickness and the temperature of the moderator material was obtained. Optimization of the detection system and the

cold neutron moderator system is planned. A multilayer system is proposed to be used as a moderator, similar to the beam shaping system for BNCT, consisting of the following components: a titanium fast neutron filter, a graphite neutron reflector located along the neutron path to minimize neutron losses, and a heavy water neutron moderator at a temperature less than 73 K. This work presents the results of the study demonstrating the possibility of generating cold neutrons at the compact accelerator-based neutron source at the Budker Institute of Nuclear Physics. This research was funded by Russian Science Foundation, grant number 19-72-30005.

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ID:45 - The BNCT neutron spectrometer NCT-WES: the NPL experimental validation campaign

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To monitor the neutron beam produced for the BNCT therapy, a directional neutron spectrometer called NCT-WES (Neutron Capture Therapy Wide Energy Spectrometer), conceived as a spectrometric beam monitor in neutron capture therapy, was designed and prototyped. As other types of single moderator neutron spectrometers, NCT-WES condenses the functionality of Bonner Spheres in a single moderator embedding multiple thermal neutron detectors in previously optimized positions. NCT-WES is a polyethylene cylinder with 36 cm diameter and 40 cm height, to achieve a sharply directional response, the sensitive part is shielded with a thick barrier made of polyethylene and borated rubber, except in the direction identified by the collimating aperture. The size, geometry, materials, and detector locations were previously optimized to emphasise the spectrometric capability in the epithermal range. Pulse-type thermal neutron detectors, consisting of 1 cm2 silicon p-i-n diodes covered with 6LiF were used as internal thermal neutron detectors. As this spectrometer is expected to routinely operate in clinical epithermal neutron beams, an experiment was organised to validate its response in the reference monoenergetic epithermal neutron beams available at NPL (National Physical Laboratory - Teddington, UK). After exposure in the 71.5 keV, 144 keV, 565 keV, 842 keV and 1200.4 keV monoenergetic beams, the experimental response was compared with the simulated one, allowing estimating in ±0.5 % the overall uncertainty of the simulation model in the epithermal domain.

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ID:62 - Study of the biological effects in glioblastoma cell lines after exposure to low and high LET radiation appearing in BNCT therapy

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The essence of Boron Neutron Capture Therapy is the reaction between 10B and thermal neutrons. In such a capture reaction, high LET (Linear Energy Transfer) particles, 4He and 7Li, are released. However, the radiation field produced in BNCT consists of different LET components. High LET protons are released in 14N(n,p)14C reaction of thermal neutrons with nitrogen and through collisions of fast neutrons with hydrogen nuclei 1H(n, n')p reaction in tissues. In contrast, low LET -rays are released due to thermal neutron capture by hydrogen in the (1H(n,)2H) reaction [1]. For such a complex mixed radiation, it is essential to study the different components to understand the irradiated cells' biological response.

Glioblastoma is the most common, most malignant, and difficult to treat among brain tumours [2]. Two human glioma cell lines which differed in their intrinsic sensitivity to ionizing radiation (radiosensitive M059J and radioresistant M059K) [3] were chosen for preliminary research with high and low LET BNCT mixed radiation field components. Both cell lines were irradiated with a surface 241Am alpha particles source at the Heavy Ion Laboratory at the University of Warsaw. This source allows for homogenous irradiation of cell samples. Accurate determination of the alpha particle's energy loss in irradiation system due to the its geometry is crucial in radiobiological experiments. The irradiation time required to obtain the corresponding cellular αradiation doses was estimated from Monte Carlo simulations using the MCNP6.2 code [4]. The simulation results agree with the measurement of the energy spectrum of the α-particles emitted from the source for an analogous geometry to the radiobiological experiment. Detailed dosimetric calculations with preliminary biological test results will be presented.

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ID:68 - Using RBS for in situ characterization of BNCT lithium targets

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The lithium target [1] is an important component in accelerators used for BNCT and is necessary for the generation of neutrons in ^{7}Li(p,n)^{7}Be reactions. During operation, the lithium target is irradiated by a high-intensity proton beam with a power density of more than 250 W/cm^2. Protons produce radiation damage in the substrate material of the target known as blistering [2]. Chemical reactions of lithium with residual gas, hydrogen and substrate material are also possible. All of these phenomena can reduce the efficiency of neutron generation. This paper describes the application of the Rutherford backscattering (RBS) method to study changes in the composition of a lithium target during irradiation with a proton beam. The advantage of this method is that it can be used in situ, i.e., using the same proton beam for RBS as for neutron generation. The method was tested at the VITA [3] accelerator at BINP. Calculations of the backscattered proton spectra were performed using Simnra v.7.03 and were compared with measurements. A peak in the backscattered proton spectra associated with oxygen indicates that the thickness of the lithium oxide layer on the target surface gradually increased during operation. There were also indications within the spectra that the substrate material (copper in this case) penetrates into the lithium layer as the power density increases and the lithium melts. Neutron flux reduction due to impurities in the Li-layer was estimated using SRIM-2008.04 and compared with measurements.

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ID:69 - Removal-Diffusion theory to calculate neutron distributions for dose determination in BNCT

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This paper solves analytically the one-dimensional multigroup removal-diffusion RD equations for monodirectional neutrons impinging perpendicularly on a semi-infinite media. For this work the scattering cross sections, neutron removal cross sections and neutron diffusion coefficients were derived using curve fitting. The neutron flux distributions were obtained for two energy groups which are used in BNCT. Dose calculations based on RD theory may be fast and accurate for BNCT treatment planning.

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ID:75 - Development of a compact multi-elements activation neutron spectrometer for BNCT

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The need of neutron spectrometry techniques for beam QA purposes as well as for comparing different facilities and accelerator types is a well-known topic in the Boron Neutron Capture Therapy (BNCT) community. In the framework of the INFN project ENTER_BNCT an activation spectrometer with an isotropic response, called NCT-ACS (NCT-Activation-Compact-Spectrometer), is under development.

The spectrometer consists of a set of activation foils (In, Au, Mn, Cu, Na, Cl, V, Ti) placed inside a moderator sphere of 2 cm radius. Each element presents its capture resonance at different energies ranging from the thermal to the epithermal region. The response interval ranges from thermal up to 100 keV. The device shows an isotropic response due to its geometry and it will be able to work in a single exposure and gamma-reading phase, allowing to reduce the total measurement time. Indications about the neutron energy distribution are derived by unfolding the activation data.

This contribution describes the most relevant results of the extensive simulation work and of the first measurement campaigns. Simulations were performed with the MCNP6 code to choose the device geometry and its materials composition. The measurements were carried out with the NCT-ACS prototype geometry at the LINAC-based thermal and epithermal neutron sources of the University of Torino (Italy) which offer a thermal and an epithermal isotropic neutron field that is known within 2-3% thanks to a well calibrated TNRD detector coupled with a BSS system. The activated elements have been analyzed using a HPGe detector. The reconstructed spectrum for the epithermal neutron field is comparable to the BSS measurements and can be considered as a first proof of the novel concept capability.

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ID:83 - Measurement of the ^{14}N(n,p) reaction at n_TOF – CERN: Implications in dosimetry of BNCT

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In boron neutron capture therapy, dosimetry calculations play a fundamental role when designing a treatment plan. The International Commission on Radiation Units and Measurements (ICRU) recommends that the delivered dose should have less than 5 % deviation from the prescribed dose, in whatever form of radiotherapy, including BNCT. In this field, one of the sources of uncertainty in dosimetry comes from nuclear data used in dose computations, but also in neutron transport simulations needed to compute the neutron fields in the irradiated region. The largest contribution to dose due to low energy neutrons in human tissues is nitrogen, by means of the ^{14}N(n,p) reaction. There have been some previous measurements of the cross-section of this reaction in the past, but there are disagreements between the data exceeding the 10 %. For this reason, and in order to reduce the uncertainties in this cross-section and dose estimation in BNCT, the ^{14}N(n,p) reaction cross-section was measured at the n_TOF Facility at CERN. The measurement used the time-of-flight technique and two types of detection set-ups: one in-bean (MicroMegas) and one off-beam (DSSSD). The measurement allowed the determination of the cross-section in the range from 8 meV to 800 keV in a continuous measurement for the first time, reaching from below thermal energy to the resonance region (above 400 keV for this reaction). We have found that the cross-section at the thermal point, which is the most relevant for BNCT, has a value of 1.809±0.045 b. The uncertainty in the thermal cross section is below 2.5 %, complying with the ICRU recommendations. The value is in line but slightly lower (-1 %) than the last ENDF evaluation. The difference with the evaluated cross-section from JENDL is larger (-6.6 %). A series of simulations have been carried out in order to test the implications of this new value of the cross-section, including effects in the neutron transport and the dose computations. New computations of the Kerma Factors for human tissues have been made. The repercussions of this measurement in BNCT will be presented.

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ID:85 - The Design of γ-ray Spectrometer for BNCT Therapeutic Beam

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As a binary targeted therapy, BNCT can selectively induce apoptosis of cancer cells without damaging normal tissues, which is one of the ideal methods to treat cancer. BNCT involves a wide range, is a comprehensive subject, there are still many problems to be solved. Due to the difficulty in the experimental measurement of gamma energy spectrum, the relevant research is less, but with the development of related supporting technology, it plays an increasingly important role in the development of precise treatment plan. In order to measure and master the fine gamma spectrum, the HPGe detector and shield are used to measure directly on the treatment beam to reduce the measurement error and improve the accuracy of the results. The shielding materials are polyethylene, tungsten and lead. And the structure is optimized by Monte Carlo simulation program.

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ID:90 - Overlapping inspection of human tissue and collimator in BNCT planning of radiotherapy

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An important step in developing a BNCT treatment plan is to determine the angle and orientation of the collimator relative to the patient. An important prerequisite for an acceptable treatment plan is that the collimator does not overlap the patient. In the previous BNCT treatment planning system (such as PHORPlan), it can only judge whether the voxel grid overlaps with the collimator, but cannot judge whether the collimator overlaps with human tissue. This is acceptable if the collimator only overlaps the air portion of the voxel grid. But if the collimator overlaps with human tissue, this is obviously unacceptable. If this problem is discovered after the dose calculation is completed or even when the position is set, the treatment will not be carried out smoothly. In addition, prior to the dose calculation, the radiation source information required for the calculation needs to be given. Usually the radiation source is located at the entrance of the collimator (BSA side) or the exit of the collimator (patient side). In terms of computational efficiency, the radiation source at the exit of the collimator is closer to the patient, so the dose distribution can be calculated faster. However, if the patient tissue partially protrudes into the collimator, the dose calculated using the radiation source at the exit of the collimator is inaccurate. At this time, the position of the source needs to be adjusted, and the radiation source at the entrance of the collimator needs to be used for calculation. Both of the above problems should be discovered and corrected before dose calculation. In response to these two problems, the treatment planning system NeuMANTA has made corresponding treatments. For the first question, after determining the irradiation position and angle, before using the dose calculation engine CCOMPASS in NeuMANTA to calculate the dose, COMPASS will traverse all non-air areas in the voxel grid to determine whether it overlaps with the collimator. If there is no overlap, continue to calculate the dose distribution; if there is overlap, suspend the calculation and prompt the user where the overlap occurs, and remind the user to change the irradiation parameters. For the second question, if the radiation source at the exit of the collimator is used to calculate the dose distribution, the air part contained in the collimator is included in the collimator part during modeling, and then it is judged whether the human tissue overlap with the collimator (and air inside the collimator) . If overlap occurs, the calculation is suspended and the user is prompted that some human tissue protrudes into the collimator or overlaps with the collimator, and the user needs to make a new treatment plan. In this way, problems can be detected in time before the dose calculation is performed so as not to delay the patient's treatment time.
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ID:98 - Development of the extended collimator in BNCT for Head and Neck cancer

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Boron neutron capture therapy (BNCT) is a new radiation therapy modality that combines neutron beam with a boron drug to selectively destroy cancer cells while leaving normal cells almost unaffected. The iBNCT project, led by an industry-academia-government collaboration team headed by the University of Tsukuba, is dedicated to the development of a linac-based neutron source device which is well appropriate for boron neutron capture therapy. The demonstration device, iBNCT001, has been completely produced and is targeted for clinical trials in malignant brain tumors, Head and Neck cancer, and skin cancer in the near future. At present, we are going to conduct non-clinical studies, which is a necessary step before clinical trials could be considered. Initially, normal type of collimators without extension beam aperture was constructed. After evaluating the beam performance in the physics characteristic measurements, it was found that iBNCT001 had a high neutron intensity, so an additional extended type of collimator was considered to be developed. This extended beam collimator can avoid the effect of interference from the patient's shoulder during BNCT of Head and Neck cancer, which has a beam aperture protruding 10 cm

from the surrounding wall. Three types of this kind of collimator with the diameter of 10, 12, and 15 cm apertures have been devised and produced, each of which is now being tested for their performance and properties. Typically, with the collimator protruding from the wall, the neutron intensity will decrease as the distance from the neutron source becomes farther, and thus the irradiation time should be prolonged correspondingly. The boron drug (BPA) currently in use requires irradiation to be completed within one hour. Therefore, even with the application of an extended collimator, it is important to ensure that sufficient neutron intensity can be generated to finish the treatment in less than one hour. Based on the results of the measurements with a water phantom, in the case of the extended type of collimator, the two-dimensional distribution of thermal neutron flux in the phantom is almost the same as that of the normal type. The maximum intensity of thermal neutrons in the phantom applied with the normal collimator was approximately 1.17×109 (n/cm2/s), and the required irradiation time was evaluated as approximately 30-35 minutes. While the maximum intensity of thermal neutrons was approximately 7.6×108 (n/cm2/s) when using collimators with the type of extended beam apertures of 12cm diameter. Thus, with the extended beam aperture collimator, the intensity of thermal neutrons in the phantom has reduced to about 65% of that of the normal type, and the irradiation time is expected to be prolonged to about 50 minutes. This is because the neutron intensity emitted from the beryllium target of the iBNCT001 device is sufficiently high so that the generated thermal neutron intensity around the tumor region in the body is guaranteed to complete the treatment within 60 minutes even when applying this extended collimator. This could eliminate the concern about the concentration of boron drugs during irradiation. Therefore, we believe that the application of the extended collimator together with the iBNCT001 device can be expected to be utilized in the practical treatment for Head and Neck cancer patients in the future.

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ID:104 - Monte Carlo simulations and in-vitro experiment to study if β-amyoid aggregates in Alzheimer's disease can be damaged by low energy neutron capture reactions

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The NECTAR project fits into the BNCT scenario proposing an innovative idea on the use of NCT principles in a very different background. NECTAR (NEutron Capture Enhanced Treatment of neurotoxic Amyloid aggRegates) project was funded by the European Commission and it aims to study the effectiveness of low-energy neutron-induced capture reactions in the degradation of β-amyloid (Aβ) protein aggregates involved in Alzheimer's disease (AD).

AD is a neurodegenerative disorder able to inhibit the proper functioning of the nervous system cells. One of AD main aspect is the overproduction of the β-amyloid protein with its subsequent aggregation and accumulation in the brain's extracellular matrix. Aggregates vary in size and shape from oligomers (spheres with a radius of a few nm) which bind to form fibrils (chains tens of um in length) up to plaques (spheres with a diameter of a few um). The efficacy of NCT should be made possible due to the ranges of charged secondaries produced by the neutron capture reactions on the B-10 and Gd-157 isotopes that couple well with the size of the protein aggregates, causing them to be completely damaged. This local action is assumed to combine with that of the gamma produced by the very same reactions which, acting over a long range, are expected to activate the glia cells causing an inflammatory response and thus promoting the Aβaggregates clearance. Both the intra-aggregate and the long range actions of the mixed radiation field created after the neutron capture reaction are the main topics of investigation of NECTAR.

The idea of the NECTAR project arose on the basis of previous studies. Research have been investigated the effectiveness of conventional radiotherapy against AD: this idea started from the clinical evidences of the effectiveness of conventional radiotherapy on Tracheo-bronchial-amyloidosis (TBA), a disease similar to AD characterised by the accumulation of a form of amyloid in the tracheo-bronchial

tree. Several patients with TBA have been treated with conventional radiotherapy and showed a significant reduction in protein aggregates[1] so that X-ray irradiation is presently the elective treatment to patients not eligible to invasive procedures. Based on this result, a study was started with the aim of verifying the effectiveness of this treatment on AD patients by appropriately adapting the doses delivered to the brain, highly radiosensitive organ. Few experiments were conducted first in vitro and then in vivo on AD murine models: the former showed no results, instead of the latter where a significant reduction in protein aggregates was observed in the absence of side effects on the animals[2,3]. On the other hand, a pilot study was conducted on a cohort of AD patients: they were subjected to several conventional CT scans and positive effects on the patients' behaviour and memory were observed[4,5].

The talk aims to present the first steps that have been taken within the NECTAR project. In particular, the results of the first in vitro irradiations conducted inside the thermal column of the University of Pavia's nuclear reactor, Triga Mark II, accompanied by a conspicuous computational activity conducted through various Monte Carlo codes on a micro- and marco-scale.

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ID:108 - Developments towards an adequate description of the dose-response relationship in the context of BNCT glioblastoma treatments

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Glial tumors constitute the most common group of intracranial tumors and among them, glioblastoma multiforme (GBM) stands out for its malignancy, rapid progression and resistance to conventional therapeutic treatments: irradiation and chemotherapy after surgery [1-2]. This tumor is characterized by glial hypercellularity, atypical nuclei (nuclear pleomorphism, multinucleation, coarse nuclear chromatin), visible mitotic activity and prominent vascular proliferation with endothelial hyperplasia, often so intense as to cause vascular obstruction and thus abundant areas of tissue necrosis that in turn act as a hypoxic stimulus inducing angiogenesis [1-3]. Despite improvements in diagnostic modalities and the use of intensive multimodal therapies including also surgery, survival time remains less than one year. In this context, BNCT is particularly interesting for the treatment of infiltrating brain tumors: being a biologically cell-directed type of radiotherapy, its application exerts deleterious effects on tumor cells and not on the surrounding healthy tissue, improving local tumor control and patient survival. The total absorbed dose delivered to tissues with BNCT is a consequence of a mixed field of radiations with different biological efficacy. The complexity of this field means that it is difficult to predict the therapeutic effect for a given total absorbed dose. It is therefore necessary to translate the BNCT dose to a dose delivered with conventional photon radiotherapy, for which the dose-effect relationship is known. The general objective of this work is to contribute to a better understanding of the relationship between the therapeutic effect and the dose delivered in BNCT, by optimizing existing models for calculating the isoeffective dose to photons in GBM patients. In particular, the dosimetry of the BNCT treatments carried out to date for this pathology has been based on the weighted dose calculation model with fixed values of relative biological effectiveness (RBE). Gliosarcoma, a primary tumor of the nervous system that originates in the

brain or spinal cord, is considered a variant of glioblastoma. Although gliosarcoma represents a distinct clinical entity, given its unique histological composition and molecular features, treatment is generally the same standardized approach used for glioblastoma. At the moment, radiobiological parameters derived from preclinical studies of gliosarcoma are used for the treatment of glioblastoma. Moreover, the weighted dose model has led to results not consistent with the observed clinical outcomes. This work proposes to extend the isoeffective dose model for the determination of dose in photon equivalent units in glioblastoma patients treated with BNCT. Starting with a macroscopic dose study, the aim is to enlarge the formalism including experimental data on boron intracellular microdistribution. For this purpose, cell survival curves were constructed as a function of absorbed dose using the human glioblastoma cell line U87. Monolayer cultures were irradiated with a Co-60 photon source and with thermal neutrons at the University of Pavia (Italy) . Based on the dose-response curves, the radiobiological parameters of the model were determined. The mentioned model was used to calculate the dosimetry of a case of a GBM patient. The obtained results were compared to those derived from the existing model based on gliosarcoma data, to assess the impact of the radiobiological parameters of different tumor types on the calculated doses. Experiments of neutron autoradiography are ongoing to obtain information on the distribution of boron using BPA in the nucleus and cytoplasm. Preliminary results will be shown. Reference [1]. Escobar A. Rev Mex Neuroci 2002; 3: 21. [2]. Muñoz J et al., An Sist Sanit Navar 2000; 23: 265. [3]. Stark AM et al., J Neurol Neurosurg Psychiatry 2003; 74: 779.
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ID:113 - Current status of BNCT for FDS group

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Boron neutron capture therapy (BNCT) is a cell-level accurate cancer treatment technology which combines the radiotherapy and targeted drugs. BNCT especially suitable for the treatment of the diffusion, infiltration, transferred or other cancers which cannot be treated with traditional methods.

Based on over three decades of neutron theory and technology research, FDS group has developed the accurate neutron therapy system, with the world leading parameters and advantages of short treatment time, high treatment accuracy (cell level), high level safety. The accurate neutron therapy system developed by FDS Group has been settled in the Hospital, and the Neutron Medicine Center is under construction. An international high-level hospital for cancer diagnosis and treatment will be built to provide tailor-made medical services for the majority of patients.

Meanwhile, FDS Group is negotiating for cooperation with more than 10 hospitals in China. China Neutron Therapy Collaborative Innovation Platform was established by FDS Group to jointly carry out neutron therapy clinical trials and applications; and to promote the development of advanced medical equipment, new drugs, innovative diagnosis, treatment methods, etc.
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ID:115 - Image Reconstruction with Limited-view-angle Projection Data for BNCT-SPECT Establishment of the Mock-up System and Validation of the Response Function

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Boron Neutron Capture Therapy (BNCT) is expected to be a new radiation therapy, and researches on various issues are still in progress. One of the unsolved issues is the development of a new system to measure the treatment effect of BNCT in real-time, and there are high expectations for a method to measure gamma rays emitted promptly via boron-neutron capture reaction from outside of a human body and to reconstruct the images in a SPECT-like manner (BNCT-SPECT). 94% of 7Li produced by 10B (n, α)7Li reaction is in an excited state (7Li*) and emits a 478keV prompt gamma-ray by the transitions to the ground state with a half-life of about 10-14 s. Because the BNCT-SPECT system measures the spatial distribution of this 478keV gamma-ray intensity. Because the number of 478keV gamma-ray is proportional to that of 10B (n, α)7Li reactions, which directly indicates the therapeutic effect, however, several difficult problems should be resolved for the development of the BNCT-SPECT system. One of

the important issues is the projection angle limitation of the measurement device. In a typical SPECT system, in which the projection angle range of the detector group is up to about 360 degrees at most. Nevertheless, in BNCT-SPECT, we must set up the patient's body on the surface of the neutron exit wall, and the angle available for the radiation measurement is limited to less than around 180 degrees. Therefore, Fourier image reconstruction methods that require projections from at least 180 degrees directions cannot be applied to BNCT-SPECT. To solve this problem, we are trying to develop a new successive approximation image reconstruction method based on Bayesian estimation, which is valid even under severe conditions specific to BNCT-SPECT and finally demonstrates the BNCT-SPECT. In this study, we perform mock-up experiments and MCNP simulations to obtain limited-view-angle projection data and the response function with which we can reconstruct images successfully. At first, we developed the image reconstruction method with Bayesian estimation to solve the problem that artifact is seen in the reconstructed images compared with the true images. Because the projection angle should be smaller for better results due to the design constraint, which is less than 180 degrees, and the detectors' moving angle is less than 90 degrees, we must find the most appropriate moving angle by MCNP simulations giving the most accurate result and then examine a filter that will prevent artifacts from making the reconstructed images match the true image better. Secondly, we constructed a mock-up system to the investigate experimental specifications for the BNCT-SPECT system development, in order to validate the response function of the measurement system of the BNCT-SPECT evaluated by MCNP5However, the mock-up system cannot reproduce the actual accuracy of a real BNCT-SPECT system because the source intensity in the mock-up experiment is too weak compared to the real one, if we measure with designed detectors shooting from the moving angle we decided. So, we had to establish the experimental system that has the same statistical accuracy and signal-to-noise ratio as the real BNCT-SPECT system. For this purpose, the mock-up system was modified by changing the position of gamma-ray sources so as to reproduce the actual accuracy of the designed BNCT-SPECT. We focus on the second objective above in this study, and in conclusion, we have established an experimental mock-up system that can reproduce actual accuracy and the response function was verified with the mock-up system. We then finally develop a reliable image reconstruction system for BNCT-SPECT.

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ID:124 - Design, engineering implementation, and beam parameters of clinical BNCT neutron beam

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Boron neutron capture therapy (BNCT) is a binary radiotherapeutic modality that combines boron containing agent with neutrons of suitable energy. Neutron beam is one of the prerequisites for BNCT, which is closely related to the dose performance and counts for the quality and safety of treatment. Therefore, a high-quality neutron beam is required, and the design of neutron beam is critical for a BNCT system. In this report, the basic principle and several key considerations of BNCT neutron beam design are presented, including neutron energy, intensity, divergence (J/) of neutron beam, background contamination, and other performance parameters. Besides, the engineering implementation of neutron beam is particularly important, which should be fully considered in the design stage. More engineering implementation considerations will be detailed in the report, such as neutron activation problem, radiation leakage and structural support. Finally, we also give the recommendation parameters and its basis for neutron beam design according to our study results.

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ID:125 - Characterization of the hydrauic rabbit in the Maria Research Reactor for biomedical irradiation in BNCT therapy.

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The hydraulic transport system, or hydraulical rabbit, is used to introduce samples into the reactor while it is in operation. Samples are inserted in sample carriers. Rabbits are used in nuclear reactors to expose samples of materials to the radiation and neutron field of the nuclear reactor and to take them out again to a receiving station after a predetermined period of time. Such a system has been characterized for the irradiation of biological samples, in vitro tests and carriers of boron atoms used in BNCT therapy. The key issue is still difficult to generate and control beams of neutrons of therapeutic quality. For this purpose, we characterized the physical and biological properties of the hydraulical transport system and optimized the system for biological research.

A special problem occurs when it is required to treat the sample with low doses and the time required must be short to convey the sample out of the reactor and to the receiving station it must be very short. Time is measured by a specially designed measuring system. In particular, the time required to take the sample out of its container and to prepare for further research (e.g. clonogenic test, sample fixation), is important. The doses obtained are in the range of 1.5-7 Gy.

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Dosimetry

ID:15 - High-accuracy dose calculation for brain tumor BNCT treatment plan with NECP-MCX

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Boron Neutron Capture Therapy (BNCT) is an effective treatment method for brain tumors with limited damage to normal tissue. It destroys tumor cells with alpha particle produced by B-10 neutron capture progress. In the BNCT treatment operation, the formulation of the treatment plan directly affects the treatment duration and the treatment effect. Accurate and efficient prediction of the dose distribution with the treatment plan system (TPS) is the premise to perform a successful BNCT treatment, and the core of the TPS is the dose solver engine. The Monte Carlo method is widely used nowadays due to its high accuracy. In this paper, a new Monte Carlo neutron transport code NECP-MCX developed by NECP laboratory is used to perform the dose calculation of a brain tumor model. NECP-MCX uses CSG-based detailed geometric modeling, with continuous energy point-wise cross-section data based on the ENDF/B-VIII library. The hybrid Monte-Carlo-Deterministic method is employed to reduce the variance of the results. The dose of target region and the dose distribution is calculated. The results are compared with those of the fast Monte Carlo solver SERAMC in the SERA treatment planning system. The accuracy of the results is higher than SERAMC. This research verifies the feasibility of NECP-MCX as the dose calculation engine of the TPS.
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ID:44 - Measuring the near-target neutron field of a D–D fusion facility with the novel NCT-WES spectrometer

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A new directional neutron spectrometer called NCT-WES (Neutron Capture Therapy Wide Energy Spectrometer) was recently developed within the INFN ENTER_BNCT project. This device constitutes a more compact and portable alternative to state-of-the-art directional neutron spectrometers. The device was used for the first time to characterise the near-target field produced by an accelerator-driven D–D fusion neutron source. NCT-WES operates as a "parallelised" Bonner spheres spectrometer, embedding six semiconductor-based thermal neutron detectors in a cylindrical moderator. Owing on a cylindrical collimating aperture, the device exhibits a sharply directional response. To account for the non-uniform irradiation condition experienced in the near-target field, a dedicated NCT-WES response matrix was developed. The neutron spectrum at 0 from the D–D neutron target, determined by means

of the FRUIT unfolding code, is coherent with that previously derived with Bonner spheres. NCT-WES proved to be a promising device for angular spectrometric characterisation of neutron-emitting targets.

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ID:47 - Doses-distribution measurement for boron neutron capture therapy in a water phantom using a scintillator detector

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With the increasing number of cancer patients around the world, scientists in various medical, biological, chemical, physical and engineering disciplines are working to develop treatments and methods to help eliminate this disease. Problems are also increasing in mitigating the side effects of these treatments on the human body and reducing the duration and cost of treatment. Currently, there are various types of treatment such as chemotherapy, surgical, genetic, viral, microwave radiation, radio frequency radiation, particle radiation therapy, high intensity focused ultrasound beam therapy (HIFU), magnetic nanoparticle therapy and others. Particle radiation therapy is the most common type of treatment, as can be performed by using external radiation therapy (proton, photon, neutron or ion beam therapy) or internal radiation therapy (radioisotope therapy). In some cases of cancer treatment, such as brain gliomas (malignant brain tumor), skin cancer (melanoma), the treatment has not been completely successful. After additional research, it was found that Boron Neutron Capture Therapy (BNCT) could be an effective and successful treatment for these cases. For this purpose, a compact accelerator-based neutron source has been developed at the Budker Institute of Nuclear Physics in Novosibirsk, Russia. BNCT treatment planning includes determining the directions and fluxes of neutron and gamma radiation and analyzing the ratio of the distribution of the dose of radiation and boron in the patient's body to ensure the possibility of optimal distribution of these doses, consistent with the necessary and taking into account dose limits for tissues in order to ensure efficacy and safety treatment for all patients and operators. In this study, we used a neutron source developed at BINP and two neutron beam shaping assembly, one with a magnesium fluoride moderator and one with a plexiglass moderator. The distribution of boron dose and gamma-ray dose within a water phantom is measured using a detector with an optical fiber readout, which includes three different sensors (the first based on a plastic scintillator enriched with boron, the second based on a simple plastic scintillator, and the third having no scintillator at all). The experimental results are presented and features of these beam shaping assemblies are discussed. Acknowledgments: This research was funded by Russian Science Foundation, grant number 19-72-30005. References: Taskaev S. et al. Neutron source based on vacuum insulated tandem accelerator and lithium target //Biology. – 2021. – . 10. – №. 5. – . 350. Zaidi L. et al. Beam shaping assembly design of 7Li(p,n)7Be neutron source for boron neutron capture therapy of deep-seated tumor //Applied Radiation and Isotopes. – 2018. – V. 139. – P. 316-324. Bykov T. A. et al. Evaluation of depth-dose profiles in a water phantom at the BNCT facility at BINP //Journal of Instrumentation. – 2021. – V. 16. – №. 10. – P10016. Sadeghi M. et al. External and internal radiation therapy: past and future directions //Journal of cancer research and therapeutics. – 2010. – V. 6. – №. 3. – P. 239. Menéndez P. R. et al. BNCT for skin melanoma in extremities: Updated Argentine clinical results //Applied Radiation and Isotopes. – 2009. – V. 67. – №. 7-8. – P. S50-S53. Nakagawa Y. et al. Clinical results of BNCT for malignant brain tumors in children //Applied Radiation and Isotopes. – 2009. – V. 67. – №. 7-8. – P. S27-S30.

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ID:52 - Measurement of the spatial distribution of neutrons and gamma radiation in a water phantom

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In this work spatial distribution of neutron and gamma radiation in the water phantom is measured at the intense accelerator-based neutron source at the Budker Institute of Nuclear Physics [1]. The water phantom made of 8 mm thick polycarbonate filled with water was used to simulate a human head. The outer diameter of the water phantom is 313 mm and its length is 330 mm [2]. To measure the neutrons and gamma radiation the scintillator-based detector was used. It consists of polystyrene-based plastic scintillators [3]: one enriched with ^{10}B isotope and another without boron. The scintillator with ^{10}B is sensitive to gamma and neutrons, without boron is sensitive only to gamma. Simultaneous operation of two scintillators enables more accurate extraction of the neutron contribution. The spatial distributions of neutron and gamma radiation in the water phantom at different energies are experimentally determined with the scintillator-based detector. The experimental data were compared with the Monte Carlo simulation of neutron transfer made by the NMC program. Acknowledgments This research was funded by Russian Science Foundation, grant number 19-72-30005. References 1. S. Taskaev, E. Berendeev, et al, Neutron source based on vacuum insulated tandem accelerator and lithium target, Biology (2021) 10, P. 350. 2. T. A. Bykov et al. Evaluation of depth – dose profiles in a water phantom at the BNCT facility at BINP. JINST (2021) 16, P10016. 3. T.A. Bykov et al, Initial trials of a dose monitoring detector for boron neutron capture therapy. JINST (2021) 16, P01024.
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ID:53 - Prompt gamma imaging for BNCT using a Compton camera

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During the neutron capture reaction with boron, there is a high chance that a 478keV prompt gamma ray will be produced. If the production vertices of these photons can be located and imaged, the density of the vertices could be used to infer the dose delivered to the patient. Previously, research into methods for detecting these prompt gamma rays has primarily focused on single-photon emission computed tomography (SPECT) systems, which require collimation of the incident photons. This collimation reduces the number of photons that can be used for the dosimetry measurements, and these reduced numbers could increase uncertainties on the inferred dose. This research project investigated a potential method for imaging the prompt gamma rays during BNCT, using a Compton camera, which does not require collimation. The basic principle of a Compton camera relies on the photon Compton scattering in one detector and being detected via photoelectric absorption in a second detector, and an energy measurement being obtained for both interactions. The angle of scatter can then be calculated using the energies measured and combining this with the axis defined by the scattering and absorption vertices, a conical surface that the photon must have originated from can be obtained. By overlapping these conical surfaces, the location of the source can be found. Typically, a Compton camera would contain separate scattering detectors and absorbing detectors, but in this project a variation of a Compton camera was investigated, where each detector in the array could act as both the scattering and absorbing detector, depending on whether an incident photon had interacted in another detector previously or not. The camera design was based off an array of lanthanum bromide (LaBr3) scintillator detectors at the University of Birmingham, with a hemispherical configuration. The initial feasibility testing of the proposed camera was carried out using Geant4 simulations, recreating and expanding on the existing LaBr3 array at the University of Birmingham. These simulations demonstrated that an extended source of boron, of diameter 3cm, could be reconstructed using clinically relevant neutron fluences. Future work is planned to further develop the simulation work, improve the reconstruction methods being used, and carry out

experimental tests of the proposed dosimetry method at the new high flux accelerator-driven neutron facility at the University of Birmingham.
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ID:57 - Fast Neutron and Gamma-ray Absorbed Dose Rate Measurements in Reference Phantom Based on Twin Ionization Chambers

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Physical dosimetry studies are the primary link in carrying out clinical applications of BNCT, and experimental measurements of relevant dosimetric quantities under reference conditions can provide the necessary data for clinical treatment planning and clinical dosimetry studies.To confirm the treatment beam quality of IHNI(in-hospital neutron irradiator), the absorbed dose rates of fast neutrons and γ-rays at different locations within the reference body model were measured using a double ionization chamber.The sensitivity of the two ionization chambers to fast neutrons and γ-rays was determined separately using a combination of experimental and monte carlo simulations.The contribution of thermal neutrons in the treatment beam to the ionization chamber readings was deducted by analyzing the difference between the readings of the two chambers in the thermal neutron field. Also, the ionization chamber was calibrated using a 60Co standard source, and its stability and repeatability were tested. The measurement of absorbed doses of fast neutrons and -rays under BNCT irradiation beam reference conditions using twin ionization chambers was explored, providing technical support for subsequent physical dosimetry studies.
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ID:65 - Detailed dosimetry of mixed fields using BNCT for skin cancer treatments

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The present work is accomplished in the context of the Argentine BNCT project that involves a Phase-II clinical trial for the treatment of skin cancer[1], carried out by the National Atomic Energy Commission (CNEA) of Argentina in collaboration with medical institutions. [1] BNCT is being studied in different countries with the aim of expanding treatment capabilities. Argentina has an open clinical protocol for the treatment of cutaneous melanoma of extremities. Irradiations are carried out at the RA-6 reactor, using the clinical beam that provides a thermal neutron flux peak of about 1x10E9 n/cm2/s at 1 cm depth. The present work addresses the study on the detailed dosimetry calculation in the main organ at risk, i.e., the normal skin, to optimize BNCT treatments. In order to understand the relationship between dose and radiation quality and possible acute and late toxicities, a more realistic dose calculation model is of high importance because the skin is often considered a dose-limiting organ of complex response. The calculation of the absorbed dose (as a result of the energy deposited by low LET electrons, intermediate LET protons, and particles alpha and high LET 7Li nuclei), is usually performed on the basis of two approximations: a) all the kinetic energy transferred to the charged particles is deposited locally (KERMA approximation) and, b) the distribution of sources of charged

particles produced by uncharged ones is spatially uniform in both tumor and normal tissue. For certain conditions, such as interfaces between different tissues or regions of interest with spatial dimensions smaller than the range of charged particles, these assumptions are not satisfied. Therefore, estimates of the dose by more detailed calculations are required. The study of the dosimetry in the skin is addressed following two approaches: the detailed computational simulation of the skin irradiation, and the experimental determination of the distribution of neutron-generated secondary particle sources in the organ. In the first case, the approach is carried out by simulations of therapeutic irradiations and calculations of the detailed dosimetry, with the transport code PHITS. The construction and modelling of a more complex geometry than the one usually used in skin calculations is proposed, that involved a complete study of the anatomy and histology of human skin, considering different material compositions and processes that determine the heterogeneous accumulation of 10-B. In the second case, the neutron autoradiography technique [2] is used to estimate the microdistribution and boron uptake in different skin structures and thus, to include this information to the developed computational model. Biological samples from a preclinical study on a large animal were used for this purpose. Both approaches are explored in two descriptions of the skin: 1) a model comprising a millimeter scale, for macroscopic studies of boron distribution and the dosimetry of the BNCT field, and 2) a model on the micrometric scale, for structural studies of the irradiated regions, and for the determination of a suitable description of the skin response to radiation and probability of effect.

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ID:72 - Gamma-Ray Dosimeter Development Using Radio-Photoluminescen Glass Dosimeter (RPLGD) in Neutron/Gamma-Ray Mixed Field for BNCT - Control of the response of RPLGD with a shielding filter -

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In BNCT, unnecessary secondary gamma rays due to neutron capture reaction are generated simultaneously together with incident neutrons. In other words, it is a mixed field of neutrons and gamma rays. Therefore, it is necessary to separate neutrons and gamma rays in order to accurately estimate the whole-body dose to the patient. In order to establish this separation method, we have proposed a "shielding filter method" in which two fluorescent glass dosimeters (RPLGD) are covered with appropriate shielding filters to control the sensitivity to neutron and gamma-ray having various energies. With the method, the true gamma-ray and neutron doses can be estimated from the two dosimeter readings. In this study, we proposed the design method of the shielding filter, and conducted the filter design for measuring gamma-ray dose in a gamma-ray field. And irradiation experiments were performed to verify the method. The response f_A of a dosimeter covered with a filter is expressed as the inner product of the gamma-ray energy dependent response function matrix R for various filter materials and thicknesses and the filter material ratio vector t, f_A=Rt. This equation was solved using Bayesian estimation method to obtain t. In the equation, f_A is air kerma coefficient (10 groups) and R has 10 rows (gamma-ray energy) × 13 columns (materials). This means that we designed the shielding filter so that the RPLGD has the same response as air kerma coefficient. Thereafter, the filter consisting of three materials was fabricated from the design result, and irradiation experiments were carried out using gamma-ray standard sources (133Ba, 137Cs, 60Co). Since previous studies had shown that gamma-ray incident angle dependence is inevitable, in this study, the material order of the three filter materials was adjusted so that the atomic number increases from the center to the outside. As the result, the dose was appropriately controlled by the filter. In the experiments, the angle dependence was examined at irradiation angles of 0, 15, 30, 45 and 60 deg. In addition, the system was precisely simulated by PHITS to compare with experimental results. First, the performance of the filter was verified by irradiation at 0 deg. using three standard gamma-ray sources. As a result, it was confirmed that the discrepancies

among experimental, PHITS, and theoretical values were generally within ±5% for all the standard sources, indicating that the filter was properly designed at 0 deg., because the design was carried out under the condition of 0 deg. incidence. Next, the angle dependence was verified using 137Cs. As a result, for all irradiation angles, simulation results by PHITS agreed to the experimental readings within the error range, and it was confirmed that the difference of experimental values for all the irradiation angles also agreed to the result of 0 deg. within ±5% error, indicating an excellent improvement in angle dependence. In the next step, experiments are planned to conduct for other gamma-ray energies with 60Co and 133Ba to verify whether the angular dependence is really improved in any energy band.

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ID:74 - Development of improved hybrid dose calculation algorithm using MC method and diffusion equation

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Clinical treatment using accelerator-based boron neutron capture therapy was started. Accordingly, efficiency in treatment planning becomes increasingly important. Therefore, we have been developing a fast dose calculation algorithm, which is a combination of the Monte Carlo (MC) method and superposition method (hereinafter called a “hybrid algorithm”). In this algorithm, the moderation of neutrons is calculated by the MC method and the thermalization is modeled as a kernel. Here, the overestimation occurred in the shallower region of a phantom because the kernel calculation in a homogeneous medium is currently adopted. Therefore, we continue the study using the diffusion equation for the calculation of the thermalization process for the improvement of calculation accuracy. We will report the study contents about the “improved hybrid algorithm”. The calculation using the hybrid algorithm was performed as follows. First, a thermal neutron flux kernel was prepared by calculating the thermal neutron flux distribution generated from the neutron source with 1 eV in the geometry filled with brain tissue. Second, the in-phantom distribution of neutrons terminated with 1 eV was derived by MC calculation with cutoff function. Finally, the in-phantom distribution was convolution-integrated with the kernel to derive the thermal neutron flux distribution. In addition, the calculation using the improved hybrid algorithm was performed as follows. First, MC calculation with the cutoff function was performed as similar to the previous hybrid algorithm. Second, a three-groups (0-0.5, 0.5-0.75, and 0.75-1 eV) diffusion equation was solved setting the source as the in-phantom distribution of neutrons terminated with 1 eV. Moreover, these calculations were performed by using the geometry where a head phantom (consisting of brain tissue, soft tissue, and bone) was irradiated from the top of it. Furthermore, the calculation accuracies of the previous hybrid algorithm and improved hybrid algorithm were verified by comparing each thermal neutron flux distribution with the result derived by full-energy MC calculation. The calculation using the previous hybrid algorithm was confirmed to overestimate the result of full-energy MC calculation in the shallow region. On the other hand, the calculation using the diffusion equation reduced the overestimation in the shallow region, compared with the calculation using the previous hybrid algorithm. However, it overestimated the result of full-energy MC calculation in the deep region in addition to the shallow region. The calculation using the diffusion equation did not reproduce the result of the full-energy MC calculation at present. The calculation code and the diffusion equation should be improved.

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ID:88 - Dosimetric study of prostate cancer using BNCT based on the Nuclear Research Reactor NUR: Monte Carlo Simulation

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Abstract: Boron Neutron Capture Therapy (BNCT) is a Binary therapy that uses the suitable neutron beam to the depth of the tumor and the Boron (B10) carrier. This technique has approved its effectiveness for the treatment of brain tumors, liver tumors as well as those of the head and neck, lung cancer, hepatoma, chest wall cancer, and mesothelioma. For BNCT to be effective, two complementary treatment conditions are essential and are as follows: a high concentration of the boron agent in the cancerous cell compared to healthy cells and a therapeutic neutron beam of high intensity (> 109 n/cm2.s). Recent works have investigated the efficacy of new molecules like the Prostate Specific Membrane Antigen (PSMA) as a boron carrier for the application of the BNCT in the treatment of prostate cancer (PCa). In the same context and with the aim of extending BNCT to the treatment of prostate cancer, our work focuses on the dosimetric study of the feasibility of using BNCT for the treatment of prostate cancer using a beam of the epithermal neutrons which was in a recent study (R. BOUMGHAR et al, 2022) optimized using the Algerian Nuclear Research Reactor (NUR), except that in this study an optimization of the collimator was made to have an opening of 4.5 cm in diameter. This study uses the Monte Carlo Calculation code (MCNP5) and the MIRD phantom that was created by researchers at Hanyang University in Korea. In this study; the MIRD Phantom has been modified by adding the prostate (represented by an ellipsoid with 5 cm in length, 4.5 cm in width and 3.5 cm in height) situated just below the bladder and the rectum situated between the sigmoid colon and the anus (With a length of 12 cm and a diameter of 6 cm). In this work, the prescribed dose to the prostate was assumed to be 60 Gy, full bladder and empty rectum were supposed too. The dosimetric evaluation of the received dose by the bladder wall, rectum wall and testis was carried out assuming a boron concentration of 65 ppm in the prostate and 18 ppm in the healthy tissue and using the appropriate materials composition and Neutron Kerma Coefficients for each organ given by the ICRU 46. This study revealed that BNCT can be successfully applied to the treatment of the PCa and provides an effective therapy in the presence of a selective Boron transporter for the prostate cancer cells. References: R. BOUMGHAR et al, 2022. Feasibility study of using the NUR research reactor for a BNCT installation and Monte Carlo optimization of a BSA. Nuclear Engineering and Design. https://doi.org/10.1016/j.nucengdes.2022.111948 ICRU 46, ICRU Report 46. Photon, electron, proton, and neutron interaction data for body tissues (1992). International Committee on Radiation Units and Measurements, Bethesda, MD.
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ID:91 - The design of mouse and rat holders used for preclinical animal experiments in XHH BNCT Center

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Boron Neutron Capture Therapy (BNCT) is binary-targeted radiotherapy, which is an ideal method for the treatment of malignant tumors. Xiamen Humanity Hospital-Neuboron BNCT Center (XHH BNCT Center) is the 1st AB-BNCT clinical and research center in China, with the AB-BNCT system designed and developed by Neuboron Medical Group. According to the current regulations in China, the safety and efficacy of AB-BNCT systems should be proven through preclinical animal experiments before clinical trials. Toxicity experiments in rats and efficacy experiments in mice are a pivotal part of preclinical animal experiments. As a medical facility for human cancer treatment, the neutron beam of XHH AB-BNCT is designed for human treatment, but not for mice and rats. If the neutron beam energy and distribution are not changed, the dose distribution in mice and rats will be poor, thus leading to a low target organ dose and a long irradiation time. Moreover, prolonged irradiation can cause dose toxicity due to high doses to some OARs (organ at risk), which is inconsistent with the reality of human treatment. Therefore, to provide an ideal irradiation condition for animal experiments, that is, to increase the dose rate in mouse tumors and rat brains, reduce the dose rate in other OARs, and reduce the dose toxicity caused by non-boron doses, especially gamma doses, it is necessary to design a mouse holder and a rat holder to moderate the radiation field, optimize the dose distribution in mice and rats, and also serve the purpose of fixing and supporting mice and rats. In this study, based on the Monte Carlo code (PHITS), a series of dose calculations were completed to design an ideal mice holder and a rat holder. Therefore, some lattice models were established by NeuMANTA TPS using CT images of

mice and rats to improve the accuracy of dose calculation. Combined with the lattice models, the dose rates of mouse tumors, rat brain and some OARs were calculated with various thicknesses of moderator in BSA and holders with various materials and structures. At last, a mouse holder composed of PMMA, Teflon, lead, and boron carbide and a rat holder composed of PMMA, graphite, lead, and boron carbide were determined. One mouse holder can hold 8 mice at a time, and one rat holder can hold 6 rats at a time. When mice and rats are irradiated in these holders if the accelerator proton energy is 2.3 MeV, the minimum tumor dose rate of mice can reach 0.027 Gy-Eq min-1 mA-1, the maximum brain dose rate of rats can reach 0.020 Gy-Eq min-1 mA-1, which can meet the needs of the XHH BNCT facility for preclinical mouse and rat irradiation experiments.

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ID:93 - Radiation safety consideration, design, and commissioning of the Xiamen Humanity Hospital-Neuboron BNCT Center

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A dozen of AB-BNCT facilities have been constructed in recent years, and many more are under construction and planning. While each type of accelerator for AB-BNCT has its own design considerations, the requirement for radiation safety is generally the common factor and it shall fulfill ALARA (as low as reasonably achievable) principle. AB-BNCT facility needs to consider thoroughly its radiation safety and protection before construction more than other conventional radiological medical equipment, because it involves a variety of rays such as protons, photons, and neutrons. As the first AB-BNCT clinical and research center in China, Xiamen Humanity Hospital (XHH) BNCT Center has successively completed its development, construction, and installation in 2021. Before its construction, we have designed the radiation shielding as well as safety measures by a large scale of Monte Carlo simulations to comply with the Chinese regulations. The core functional spaces and major equipment of XHH BNCT Center are located on the first and second basement floors. The whole facility is divided into controlled, supervised, and uncontrolled areas according to the possible exposure attributed to radiation sources. Radiation shielding in the facility and particular concerned areas has been estimated and optimized prior to facility construction, such as wall thickness, composition of building materials, room layout, residual radioactivity, etc. Based on the concept of conversation, the simulation source intensity was considered to be 1.5 times maximum output. A specially designed and developed boron-containing barite concrete was used as radiation shielding and structural material in building construction. The 1.2-meter thickness of concrete with boron-containing barite can effectively shield both neutron and gamma-ray radiations, which has been computationally evaluated and experimentally verified. For long-term consideration of radiation safety, the induced activity that involves space activity distribution and exemption factor is also investigated carefully. At present, many rounds of beam commissioning and animal experiments have been successfully carried out on the NeuPexTM AB-BNCT System designed and developed by Neuboron Medical Group. During beam commissioning, dose rates were measured at various points in the BNCT facility, including gamma-ray and neutron. The measurement results show that the radiation shielding of XHH BNCT Center is satisfactory for different beam current conditions. In addition, we performed dose calculations and measurements for target replacement and storage processes. These radiation protection measures keep staff safe. Details of these works will be provided in the presentation.

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ID:94 - Dosimetry measurements at the Finnish accelerator-based BNCT facility

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Dosimetry is integral part of quality assurance in BNCT, and a wide array of equipment is essential for neutron beam characterization. In this work, we go through the different types of dosimetry measurements at the Finnish accelerator-based BNCT facility including our equipment, measurement set-ups, novel utilization of various 3D-printed parts, and our scheme for film dosimetry.

Starting with the equipment, our primary detectors are activation foils and wires. Diluted gold- and manganese-aluminum foils are used for various measurements – like daily quality assurance, beam profile, and repeatability. As for ionization chambers, two different types are in use – argon gas filled magnesium chamber and tissue equivalent (TE) gas filled TE-chamber – which are usable for the twin ionization chamber method. As for phantoms, we have a large water tank and a cylindrical PMMA phantom. The water phantom offers a tissue equivalent environment for wide beam profile measurements, and it has un-restricted positioning for detectors. Meanwhile, the smaller PMMA phantom offers better ease of use with its convenient size, for example for daily quality assurance. With this equipment alone, a multitude of different measurement set-ups is possible.

The cylindrical PMMA phantom has removable inserts along its middle axis with locations for foils or ionization chamber. The phantom has been used to measure depth profiles with foils, but it is also excellent for repeatability and constancy tests since it can be used for simultaneous foil and ionization chamber measurements. On the other hand, the water phantom has been used for beam profile measurements in all directions with ionization chambers and activation foils and wires. 3D-prints are used in measurement set-ups for the ease of phantom and detector positioning and also as detector holders. This is especially true for the water phantom. We have developed suitable 3D-prints for ionization chamber holders which allow the chamber to be positioned further away from metal parts that undergo activation in neutron beam, and they also allow ionization chambers to be positioned in different orientations, such as parallel or perpendicular to the beam. As for activation foils and wires, we have made sample holders for profile measurements. They enhance sample positioning precision and repeatability between measurements with minimal perturbation of the neutron and photon fields.

In addition to other dosimetry methods, film dosimetry has been in development. We are planning to use Gafchromic film which is already used in traditional external radiation therapy. The Gafchromic film can be exposed with high energy photon beams but in addition it has small amounts of lithium which decays to two alpha particles after capturing an incident neutron. Hence, the resulting optical density of the film is a combination of the different beam components.

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ID:97 - A Versatile Treatment Planning System for basic research in BNCT

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A Treatment Planning System (TPS) for BNCT has been designed as a tool for basic research. A key aspect in the development of this code is versatility, allowing free parameters and subject to inclusion of new capabilities.

Our TPS extracts data from DICOM images of patients (CT, MRI and/or PET/CT), and incorporates this geometry and materials into the Monte Carlo simulation code MCNP v6.2. used as dose engine in this case. Materials and tissues are chosen taking into account Hounsfield-Unit conversions. The TPS is able to use any neutron beam previously built into MCNP as an input for the calculation of dose. Different models of dose computation can be implemented for the elaboration dose reports, which include isodose maps and dose-volume histograms. The results can be optimized to determine the definitive treatment plan.

Based on the medical images obtained from actual hospital patients, it has been possible to test the program with real cases. The cases that have been studied so far are glioblastomas, but this TPS can be adapted to different areas of the whole body. These prime tests have been done with a recently designed neutron production system optimal for BNCT of deep tumors [1] and also with a reactor-based facilities as the FiR-1. The flexibility in all the described steps of this TPS makes it relevant to basic research that are necessary for BNCT. This includes the potential application of BNCT to cancers in advanced stages by simulating treatments in real cases.

[1] P. Torres-Sanchez, I. Porras, N. Ramos-Chernenko, F. A. D. Saavedra, and J. Praena, "Optimized beam shaping assembly for a 2.1-mev proton-accelerator-based neutron source for boron neutron capture therapy," Scientific Reports, vol. 11, p. 7576, 123.

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ID:99 - Out-of-field dosimetry using validated PHITS model in clinical BNCT

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[Purpose] It is important to know the out-of-field dosimetry in clinical BNCT. In our previous work, thermal neutron flux and gamma-ray dose were validated among measurement, treatment planning system, and an independent PHITS model [1]. In this study, additional validations of PHITS model for whole-body region were performed. Also, dose of organ-at-risks (OARs) outside of the irradiation field were evaluated using the PHITS model and a computational phantom. [Methods] The BNCT treatment system NeuCure® source and its irradiation room was modeled in the PHITS. Neutron measurements by activation method of Au, In, and Al and photon dose measurements were performed for the validation. We performed three procedures of validation and evaluation: (i) validation in whole-room, (ii) validation inside body using humanoid water phantom, and (iii) dose evaluation of OARs using computational phantom. (i) The out-of-field neutron distribution was compared between measurement and simulation via reaction rates of Au foils attached at room walls. (ii) Neutron reaction rate and photon dose at 10 OAR points inside humanoid water phantom were compared between measurement and simulation via Au, In, Al and TLDs. (iii) An mesh-type reference computational phantom provided by the Internal Commission on Radiological Protection (ICRP) group [2] was arranged in the validated model with supine position. The relative biological effectiveness (RBE) -weighted doses in one-hour irradiation were evaluated for the following OARs: brain, left and right eyes, left and right salivary glands, thyroid, esophagus, spinal cord, left and right lungs, liver, rectum, and bladder. The doses were converted to equivalent dose in 2 Gy fractions (EQD2).

[Results] (i) The reaction rates of Au agreed well between experiment and simulation in 70-cm radius on the collimator side, and agreed within one digit for others. (ii) The results agreed closely between experiment and simulation, but the simulated results of photon dose at abdominal and pelvic region are slightly lower than experimental results. (iii) The median values (D50%) of EQD2 were 3.2 Gy-eq for right salivary gland, and lower than 1 Gy-eq for others. The maximum values (D2%) of EQD2 were lower than 10 Gy-eq for all OARs. These results are lower than the constraint dose used in X-ray therapy. [Conclusion] The PHITS model extended in whole-body region was validated, and the safety of the OAR dose was confirmed. In future, we establish the fundamental technology of out-of-field dosimetry in various posture using the deformability of the ICRP phantom. [Citation] [1] Hu et al., Radiat Oncol. 2021;16(1):243, [2] ICRP Pub 145. Ann. ICRP 2020; 49(3).

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ID:111 - A photon isoeffective brain dose model for BNCT based on dose–response assessment from an animal model and its impact on a retrospective analysis of glioblastoma treatment.

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In a clinical protocol, calculating and understanding the dose administered to the organs at risk is very important, since these tissues impose a limit to treatment time, and thus, to tumor dose. In particular, the brain is a major dose-limiting organ for brain cancer patients undergoing radiotherapy. Therefore, an adequate estimation of the dose to this organ is essential to minimize the potential adverse effects.

In order to relate the effects observed in clinical BNCT protocols to the corresponding results obtained with standard photon radiotherapy, a model to translate BNCT doses to photon-equivalent units is necessary. Usually, the "RBE-weighted" dose model is used for this purpose. However, this procedure has been shown to lead to overestimation of tumor doses and underestimation of the dose to the normal tissues.

The concept of photon isoeffective dose was developed and was found suitable for describing the BNCT dose in photon-equivalent units for different tissues. This concept allows calculation of a reference photon dose that is estimated to produce the same biological effect as the combination of the different absorbed doses administered with BNCT. In this work we developed a model for calculating photon isoeffective doses for the normal brain, based on the radiotoxic effects reported for an in vivo small animal model subjected to photon and BNCT irradiation. For this, we proposed suitable mathematical expressions to describe the normal tissue complication probability (NTCP) for the reference photon radiation and for BNCT, which allowed us to derive the first model to obtain the photon dose that produces the same probability of brain toxicity as the BNCT treatment.

The rat spinal cord model has been used to study the late radiation-induced effects and the biological effectiveness of photon and BNCT irradiations in the normal central nervous system. Experimental results showed that the late toxicity seen in the brain and the spinal cord following irradiation are similar. Thus, dose-response data reported for the spinal cord were used to construct the photon isoeffective dose model for the normal brain. The development of this model required selection of adequate reference data, that is, results of irradiations performed with photon energies that are comparable to those used in clinical treatments. Thus, we searched for experimental data corresponding to both single fraction and fractionated irradiations performed with the same linear accelerator as used in photon radiotherapy [1]. We then proposed a NTCP model that accounts for the differently fractionated schemes and that allow us to consider the two cellular repair times of the biphasic kinetics observed for the brain. The free radiobiological parameters were determined by robust minimization methods. Reported in vivo experiments with BNCT included beam-only irradiations and irradiations after boronophenylalanine (BPA) administration [2]. For the construction of the dose calculation model, we selected BNCT data with the normal tissue-to-blood boron concentration ratio that were most similar to those used for brain treatments. The proposed expressions of the NTCP for BNCT were used to fit the experimental data. From the obtained probability models for photons and BNCT, we derived the photon isoeffective dose model for the normal brain.

We next applied the developed model for dose calculation in BNCT treatments of malignant gliomas performed in Finland [3]. The calculated doses, compared with adverse tissue reactions expected from conventional radiotherapy, allow us to assess whether the doses are representative of the radiotoxic effects observed in clinical BNCT. We also compared the photon isoeffective doses to those obtained with the standard model. We found that the normal brain doses derived from our model are higher than those obtained with the standard model. These results may impact the treatment planning of the future BNCT protocols and enhance the understanding of the adverse effects of this therapy.

[1] Ang et al., IJROBP 13, 557-562, (1987) [2] Morris et al., Radiother. Oncol. 32, 249–255, (1994) [3] Kankaanranta et al., IJROBP 80, 369-376, (2011)

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ID:134 - Tissue uptake of novel BNCT compounds in a mouse model, with pharmacokinetic and dosimetric extrapolation to human treatment

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Increasing the armamentarium of boron delivery compounds is a widely recognized ambition in the field of BNCT. In this work we report pharmacokinetic measurements using novel boron delivery compounds with a mouse model. Boron uptake in multiple mouse xenograph tumor models, as well as blood and organs at risk, has been measured via inductively coupled plasma optical emission spectroscopy (ICP-OES) for boronophenylalanine (BPA), as well as several candidate compounds for future BNCT applications. Measurements were performed between 0 and 24 hours following bolus injection of the boron compounds. Separate experiments demonstrated tumor control for these compounds at levels comparable to, or better than, BPA when irradiated with thermal neutrons. A preliminary study of the impact of these compounds for human treatment was made by fitting these measured data to mathematical pharmacokinetic models previously validated for BPA concentration prediction within various tissue types in humans. These modified models allow the tumor and normal tissue concentrations resulting from infusion of the new compounds in a human patient to be estimated, and therefore the absolute concentrations and concentration ratios between tumor and other tissues as a function of time to be compared against those that are currently possible with BPA. Furthermore, the dosimetric impact of these differences has been evaluated using Monte Carlo dose calculation methods and beam models currently under development for the AlphabeamTM BNCT system. While this extrapolation to human treatment is contingent on multiple assumptions, these results will help to guide the design of clinical trials involving these compounds and could help to develop a framework for evaluating other compounds in the future.
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Accelerators

ID:17 - Design, Construction and Beam Commissioning of the 14 MeV Cyclotron for BNCT at CIAE

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A high-intensity compact cyclotron was designed and constructed at China Institute of Atomic Energy (CIAE), providing a 14 MeV, 1 mA proton beam for boron neutron capture therapy (BNCT). A compact four-sector magnet with deep valley is adopted, which provides high enough flutter and axial focusing. Two RF cavities are installed in the tow opposite valleys with a resonant frequency of 73.35 MHz. The high-intensity H- beam is extracted from an external multi-cusp source and injected into the cyclotron by a spiral inflector. The acceleration gaps in the central region are designed with different heights, which greatly improves the electric focusing. After 100 turns of acceleration, the H- beam reaches an energy of 14 MeV and is stripped by a carbon foil. The construction of the cyclotron is complete and beam commissioning is underway. The result shows that the current of extracted beam reaches 1 mA with a transmission efficiency of 16.5%, and the 5-hour stability test with 1 mA beam at internal probe is passed.
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ID:67 - Development of Neutron Production Targets for AB-BNCT

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Neutron beams are an essential part of BNCT. These neutron beams must fulfill certain requirements for this therapy, like a given neutron energy and neutron flux. Neutron energy of the beam has to be mostly epithermal, so as to reach the boron with thermal energies. Neutron flux must be high enough to obtain a reasonable treatment time. There are several ways to produce such neutron beams, mainly in nuclear reactors and particle accelerators. Nuclear reactors are a powerful source for neutrons and well known technology, while particle accelerators are newer as neutron sources for BNCT. They present important advantages for BNCT: feasibility to be built and operated in health centers, better radiological safety and lower cost, for instance. All these reasons have motivated the development of different accelerator and target designs, pursuing the objective of producing neutron beams that are suitable for BNCT.

The group of Accelerator Technology and Applications from the National Atomic Energy Commission (CNEA) of Argentina has been working for several years in the development of different accelerators and targets, both for BNCT and other applications. It is currently building a new Laboratory for Accelerator Development (LDA), with a strong focus on BNCT. It has already developed an operational accelerator for AB-BNCT and sold an exemplar to KIRAMS.

Several targets have been developed, some of which are intended for BNCT. These are the 13C and the 9Be targets, which produce suitable neutrons when bombarded with deuterons. Such targets have already been produced, characterized by several techniques, and tested for neutron production. Other

targets are also being developed for other applications, like deuterium and tritium targets. In this work, we present our last results and current status.
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ID:109 - Radioprotection assessment of an AB-BNCT Lab

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The Accelerator Development Lab (LDA) is under advanced construction at the National Atomic Energy Commission (CNEA), Argentina. The Lab will be devoted to developing accelerator technology for BNCT and other applications and will house a 1.45 MV Electro-Static-Quadrupole (ESQ) accelerator capable of delivering 30 mA beams of protons and deuterons. Focusing on the BNCT application, this machine will generate neutron beams through the 9-Be(d,n)10-B and 13-C(d,n)14-N reactions. We present an assessment from the point of view of radioprotection. The Lab was simulated with the MCNP code. Occupational (worker) and the public's dose delivered in routine operation were calculated. Daily operation is envisaged as an 8-hour single-shift irradiation (i.e., 8-hour continuous irradiation followed by 16-hour downtime), totalizing 2000 hours of irradiation a year. This scheme of operation fits the constraint doses adopted (1 mSv/y and 0.1 mSv/y for workers and the public, respectively). During irradiation, the dose is mainly due to secondary gamma rays generated by the neutron-induced reactions on the room walls and shielding and, to a lesser degree, on the elements of the beam shaping assembly (BSA). Neutron dose is negligible outside the irradiation room and in any place where workers and the public are allowed to stay during irradiation. The accelerator room (as well as the irradiation room) is forbidden to access when the accelerator is on. There, X-rays are generated by secondary electrons released inside the accelerator column. These electrons are produced when the beam 'halo' reaches some accelerator parts and also, when the residual gas in the column is ionized. Once released, these electrons are pulled towards the quadrupoles of the accelerator tubes where they impinge producing Bremsstrahlung radiation. Preliminary measurements were performed with a smaller prototype (240 kV) to characterize X-ray production under realistic operating conditions. After irradiation, the occupational dose is due to activated elements. The most activated ones are the BSA and the target. Activity concentrations were calculated through cross-section data and MCNP simulations. We will evaluate and present the occupational dose associated with different scenarios representing routine tasks in the presence of activated elements.
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Imaging

ID:18 - A Self-Attention ResUnet to generate synthetic CT for MRI-guided BNCT

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Background : The acquisition of boron concentration distribution, is one of the crucial phases in BNCT since boron dose is the main component of BNCT dose composition. MRI technology has been shown to be useful for boron medication localisation and pharmacokinetic evaluation, which is helpful for treatment planning. The planning system now uses computed tomography (CT) images for radiation dose calculation. Despite the significant physical differences between MRI and CT, the high entropy of MRI data indicates the existence of a surjective transformation from MRI to CT image. However, there is no specific optimization of the network itself in previous MRI/CT translation works, resulting in mistakes in details such as the skull margin and cavity edge. These errors might have moderate effect on conventional radiotherapy, but for BNCT, the skin dose will be a critical part of the dose composition.

Purpose: To create a self-attention network which could directly transfer magnetic resonance imaging (MRI) to synthetical computerized tomography (sCT) images with lower inaccuracy at the skin edge and examine the viability of MR-guided BNCT.

Methods: A retrospective analysis was undertaken on 104 patients with brain malignancies who had both CT and MRI as part of their radiation treatment plan. The CT images were deformably registered to the MRI. In the U-shaped generation network, we introduced spatial and channel attention modules, as well as a versatile "Attentional ResBlock", which reduces the parameters while maintaining high performance. We employed 5-fold cross-validation to test all patients, compared the proposed network to those used in earlier studies and used Monte Carlo software to simulate the BNCT process for dosimetric evaluation in test set.

Results: The MAE of SARU results in the head region is 67.08±15.65 for all 104 cases (five-fold cross-validation), while UNet, ResNet, and Pix2Pix results are 74.05±14.22, 71.14±18.57, and 82.57±18.09, respectively. Unet and Pix2Pix had slightly lower or similar MAE than earlier experiments. Meanwhile, Monte Carlo dose calculation results show that for all 10 test cases the calculation deviation of the sCT dose is less than 1% compared with the real CT dose, and the gamma index of 2%/2mm is greater than 98 %, which met the dose calculation requirements. This method can greatly simplify the treatment planning process of BNCT and reduce the dose risk of BNCT therapy.

Conclusion: We have developed a residual U-shape network with an attention mechanism to generate sCT images from MRI for BNCT treatment planning with lower MAE in six organs. There is no significant difference between the dose distribution calculated by sCT and real CT. This method can greatly simplify the treatment planning process of BNCT, reduce the dose risk of BNCT therapy and minimize image feature mismatch.

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ID:26 - Evaporation coefficient as a correction factor for boron quantification in histological sections through neutron autoradiography technique

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The Neutron Autoradiography technique using Nuclear Track Detectors (NTD) is widely applied to study boron microdistribution in tissue samples previously infused with a certain boron compound. For this purpose, the tissue section is mounted on an NTD. By irradiating the assembly with thermal neutrons, the 10B (n,α) 7Li reaction (BNC) takes place and the resulting αand Li particles entering the detector material cause permanent damage along their paths. This latent damage can be revealed by a chemical attack (etching) and amplified at light microscopy level, which enables their observation and quantification. Mapping the nuclear tracks allows the assessment of the spatial distribution of 10B in the biological sample and the analysis of the uptake pattern of different borated compounds.

Samples of tissue to be studied using this technique are frozen in liquid nitrogen immediately after extraction in order to avoid the migration of boron atoms from their original place, and the histological sections are obtained using a cryostatic microtome (or cryostat). In the transition to room temperature, the tissue undergoes an evaporation process that generates an increase of 10B atoms concentration in the sample. Furthermore, in the case of soft tissues, evaporation has a direct influence on the tissue section thickness which, at the irradiation moment, will be smaller than the nominal thickness set in the cryostat. Thickness of the sample determines the number of particles arriving at the NTD and consequently affects the boron quantification. For these reasons a natural amplification of the final number of tracks in the detector occurs. In order to quantify the boron concentration in the original sample it is necessary to establish correction factors that account for this effect. Since evaporation implies a loss of weight in the sample, and assuming that the quantity of boron atoms does not vary during this process, the concentration can be corrected by an Evaporation Coefficient (CEv) defined as: CEv = ms/mh, where mh corresponds to the "wet" section mass, measured immediately after the tissue is sectioned in the cryostat, and ms is the "dry" section mass, measured when the evaporation process is finished. In our laboratory, the experimental conditions for the sample mass variation measurement with a semimicro scale have been set up, and a protocol to determine the evaporation coefficients corresponding to different tissues has been established. This protocol was applied to record mass variation due to evaporation in different tissues of interest for autoradiographic analysis, in order to obtain reproducible results of evaporation curves and reference values of CEv.

In this work, measurements were carried out in normal liver, lung, kidney and metastatic lung for different species: BDIX rats, nude mice, hamsters and sheep. Moreover, different types of tissue coming from a hamster's cheek pouch oral cancer model (tumor, normal pouch tissue and precancerous tissue) were also analyzed. Distributions of the CEv values for each tissue were studied and consistent results were obtained, which allowed to establish a set of reference values. Furthermore, it was observed that rat tissue CEvs correlate with the characteristic water content measured by desiccation in lung, liver and kidney reported in the literature. These results will allow the correct quantification of boron in tissue sections through neutron autoradiography technique.

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ID:34 - IMPLEMENTATION OF AUTOMATION SYSTEM AND VISUALIZATION OF EXPERIMENTAL DATA IN REAL TIME AT THE BNCT FACILITY BINP

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An Epithermal neutron source based on an electrostatic tandem accelerator of a new type Vacuum Insulation Tandem Accelerator, and a lithium neutron generating target has been proposed and developed at the Budker Institute of Nuclear Physics for the Boron Neutron Capture Therapy the promising method for treat-ment of tumours and for other applications. This paper proposes and implements a flexible and customizable method for the operational data processing, allowing an operator and physicists to obtain and analyze the infor-mation during the experiment without the need of post-processing data. The application of it accelerates the process of obtaining informative data during the experi-mental research and automates the analysis process. Also it was proposed and implemented a process of automatic distributed journaling of the results of the experiment. As a result of the implementation of the proposed tools the productivity of the analysis of experimental data and the detailing of the experimental journal was increased the developed and implemented system of real-time data processing has shown its effectiveness and has become an integral part of the control system, data collection and data storage of the epithermal neutron source.

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ID:36 - Feasibility study of Prompt gamma-ray imaging by a Compton camera

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In BNCT, it is difficult to measure the dose to the patient, and the dose calculation by simulation also contains many error factors. Thus, the dose estimating method by imaging generation of 478 keV prompt -rays due to the BNC reaction (BNCR) is being investigated. However, there are many high-energy -rays and neutrons during treatments and they create difficulties in the measurement. In this study, we confirmed the suitability of a Compton camera to measure the BNCR. A Compton camera is an imaging device for radiation sources with Compton-scattering kinematics. A typical Compton camera consists of two types of sub-detectors and simultaneously measures scattering and absorption. It can estimate the direction of incoming -rays from the position and energy information detected by the sub-detectors. We have been developing a Compton camera for medical use and in this study, we have examined the possibility of its application to BNCT. The Compton camera has eight Si semiconductor detectors as scatterers and four CdTe semiconductor detectors as absorbers. The angular resolution measure is 6°for gamma-rays of 511 keV. Compton imaging was performed with approximately 20 g B4C powder in a plastic case (approximately $0.7 \times 2.2 \times 9.6$ cm3) and using an AmBe neutron source at Osaka university. The generated neutrons were moderated by a graphite block of 40 cm thick. The B4C target was set at the center of a water tank ($10 \times 10 \times 10$ cm3) in front of the Compton camera. The distance from the first scatterer to the center of the target was 13 cm. The measurement time was 2 h. The images were reconstructed with a list-mode maximum likelihood expectation maximization algorithm. To confirm if the data contained the signal from the target, we conducted an experiment with a graphite block of the same size instead of the B4C target. The neutron and -ray distributions were estimated by a Monte Carlo simulation with PHITS in which the thermal neutron flux at the target stage was 500 n/cm2. As a result, we succeeded in imaging the position of the B4C target. Analysis indicated that the image cannot be considered as a misidentification of artifacts. Image quality is not satisfactory and would need further improvement, even considering that the thermal-neutron flux in this study is very low compared to the treatment conditions. Smaller targets are needed to evaluate spatial and contrast resolution. However, it requires longer measurements and/or more intense neutron fields. The Compton camera contains boron, which inhibits the measurement. In addition, there are many background gamma rays, which cause a lot of dead time. All these issues need to be improved to push it up to medical applications.

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ID:49 - Machine learning based image classification in neutron autoradiography

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Knowledge of the ^{10}B microdistribution is of great relevance in the study of BNCT therapeutic protocols and boronated compounds. This is a key factor to understand boron concentration in different tissular structures and the homogeneity of tumour dose-distribution. Neutron autoradiography is an ideal technique for this task: by laying a boronated sample on top of a Nuclear Track Detector (NTD) and then irradiating the arrange with a thermal neutron flux, the reaction ^{10}B(n,α)^{7}Li (BNC) takes place and the ejected particles penetrate the detector, leaving a localized damage zone, or latent track. After a chemical process, tracks become observable under optical microscopy, and can then be translated to a boron concentration value or distribution.

Since ^{10}B concentration depends on the correct track density quantification, image acquisition and processing conditions should be controlled and verified, in order to obtain accurate results. The main criteria for distinguishing tracks from artifacts is that the former have regular geometrical shapes (circular or elliptical depending upon the angle of incidence) and more uniform grayscale values. For this reason, we developed an image classification algorithm using feature extraction as a pre-processing step to reject inadequate images.

Over 22000 BNC images were used, acquired by a variety of individuals over several years and corresponding to aqueous solutions and biological tissues with different ^{10}B concentrations. A label "Accepted" or "Rejected" was defined for each image, based on the classification criterion of an autoradiographic images expert. For each image, a set of morphological and uniformity parameters were extracted from the quantified objects (area, diameter, aspect ratio, roundness, heterogeneity and clumpiness). Six statistical parameters (mean, median, interquartile distance, standard deviation, 5th percentile and 90th percentile) were computed for each of the 6 characteristics, so 36 features, plus a label, were used to represent each image.

A series of machine learning models were evaluated for this application. The two with the highest performance are compared in this presentation: a Support Vector Machine (SVM) and an Artificial Neural Network (NN). SVM algorithm was trained with a Radial Basis Function (RBF) kernel and using cross-validated randomized search for finding the best hyperparameters. The NN was trained several times (aprox 10 minutes each time, using Google Colab) adjusting the number of neurons, layers, optimization algorithms, learning rate, among others. The final model consisted of a 3 layer fully-connected network, with 150 neurons per hidden layer. To avoid overfitting, L2 regularization, dropout and early stopping were used. Additionally, learning rate reduction was set for monitoring loss in the validation set. The final performance metrics were similar for both models: 93% for both accuracy and precision for the SVM, vs 94% accuracy and 95% precision for the NN. Based on the distribution of the predicted class probabilities, the latter had a better capacity of learning features belonging to each of the classes, so the NN was selected to perform the image verification step prior to quantification.

We have recognized the potential of including machine learning methods in our workflow, and we are planning to extend their use to different steps in the autoradiographic analysis, such as the segmentation of tissular structures, or quantification of nuclear tracks in images with cellular or tissular contours.

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ID:58 - Optical density analysis in autoradiographic images for the study of preferential boron uptake in broncho-vascular tree and its effects on lung dosimetry

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The lung is the most frequent site of metastasis for many types of tumours and for some specific types of cancer it is the only site of metastatic lesions. In Argentina, a multi-institutional project has been established to assess the feasibility of applying BNCT ex-situ to the treatment of patients with multiple lung metastases, which would allow the treatment of all tumors, regardless of their positions, shapes and sizes. The project seeks to study the feasibility of delivering a therapeutic dose to tumor tissue without exceeding the radiotolerance of the normal lung, which is the organ at risk during the proposed treatment. The proposed procedure consists of boron infusion, and irradiation of the explanted organ followed by surgical reimplant. This process requires perfusion of the organ with a conservation solution in order to preserve the organ during the treatment. Within this context, the validity of the ovine model as an adequate human surrogate in terms of boron kinetics in clinically relevant tissues has been established. Simulations of the organ irradiation inside the thermal column of a nuclear reactor and a suitable tumor control probability (TCP) model for lung cancer, afforded a promising average fraction of controlled lesions [1]. Furthermore, the therapeutic efficacy of BNCT has been demonstrated in a small animal lung metastases model [2] and the neutron autoradiography technique has been applied to quantify boron microdistribution in normal and metastatic lung from BDIX rats [3].

During a new boron biodistribution study of a normal sheep where boronophenylalanine-fructose complex (350mg/kg) was infused for 40 min, samples of lung and other tissues of interest were extracted for boron determination. ICP-OES measurements were carried out and sections of normal lung were processed to obtain autoradiographic images using polycarbonate as nuclear track detector (NTD). The sample-detector assemblies were irradiated with a high fluence (1013 n.cm−2) and etched for 4 min in order to generate track overlapping. This allowed for the analysis and quantification of the collective optical effect of nuclear tracks using optical density (OD) as the end point. The qualitative analysis of lung samples revealed a preferential uptake of BPA in the broncho-vascular tree at the microscopic level. Based on these findings, OD measurements were performed in order to quantify this trend, as it could explain potential vascular damage in normal lung after BNCT. For this, regions of interest (ROIs) were delimited in the histological images of lung and the OD in each of these ROIs was calculated in the corresponding autoradiographies. Preliminary studies showed that the broncho-vascular tree captures almost twice as much boron as the alveolar region. These results were observed in both pre and post perfusion lung samples, indicating that the uptake differences are not a consequence of the conservation process. The impact of these findings on the dosimetry of a potential BNCT ex-situ clinical setting was assessed. This information could also be of interest for the dosimetry of a BNCT treatment that involves irradiation of the thoracic cavity. [1] Farías and Garabalino et al.,Med Phys 42,4161-4173, (2015). [2] Trivillin et al.,Int J Radiat Biol 95,646-654,(2019) [3] Espain et al.,ARI 165,109331, (2020).

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ID:76 - Fundamental Study on T/N Ratio Determination by Ex-vivo Macro-imaging of BPA with A brain tumor model rat for BNCT

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Boron neutron capture therapy (BNCT) has the potential to selectively kill cancer cells at cellular level. The therapeutic efficacy of BNCT is calculated based on the concentration of boron in tissues, the boron biodistribution and the flux intensity of neutrons the patient is irradiated with. Since the technology to determine the boron biodistribution on a tissue sample at micro or macro level is still being developed, current research into the biological effects of radiation has not revealed how damage to individual types of cells contributes to overall tissue damage. In our preliminary study, we obtained the macro-image of boron on a thinly sliced brain, after administering L-p-Boronophenylalanine (BPA) to a brain tumor model rat, with matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI). The result demonstrated that BPA is localized in the invasive margin of the brain tumor even within the tumor of 5mm in diameter on the sample (patent pending). MALDI-MSI utilizes sequential mass analysis of an ionized sample and uses obtained spectral intensity and location information to generate images of the distribution of molecules. This technology has high resolution (100µm) and multi-analyte detection. However, one of the challenges associated with this method is to determine the absolute concentration of boron in normal and tumor cells, due to differences in ionization efficiency between tumor and normal tissue. Accurate calculation of the ratio of boron concentration in tumor cells (T) to normal cells (N) (T/N ratio) is extremely important for BNCT. In this study, we analyzed the difference in ionization efficiency between the tumor and normal tissue with MALDI-MSI. Finally, we reconstructed the spectral image that MALDI-MSI generated in the preliminary study, to an image that is suitable for the assessment of T/N ratio for BNCT. Before MALDI-MSI, we prepared a sample by dripping and drying a fixed concentration of BPA solution (hereinafter, this is called "standard BPA") onto a thin brain section taken from a rat with transplanted brain tumor (melanoma) . We then compared the intensities of the mass spectra of standard BPA between tumor and normal tissues on the obtained images. Dripping is a common method of applying standard solution on the sample in MALDI-MSI. However, the resulting image showed high spectrum value only in the circumference of the standard BPA spot, and no spectrum was detected around the center of the spot, resulting in a hollowing of the BPA spot. This was caused by the accumulation of boron on the circumference of the spot during the drying process of the droplet of the solution. For accurate quantification, it is necessary to suppress the hollowing of the BPA spot. Therefore, in this study, we applied spraying of standard BPA solution, because spraying forms a homologous layer of the solution. Images that MALDI-MSI generates have the characteristic that even the same amount of molecule shows different intensity between areas that possess different molecular characterization. In this study's result, the same amount of standard BPA demonstrated different intensities in the tumor and normal areas. This indicates that there may be a difference in ionization efficiency between the tumor and normal areas. Besides, spraying of standard BPA provided a more uniform dot image than that of dripping. The reconstructed image calculated with the factor for correction of ionization efficiency could suggest a more accurate T/N ratio than the original one. This hypothesis should be tested in future using liquid chromatography mass spectrometry that can measure extremely small amounts of molecules.
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ID:81 - Real-time Boron Concentration Monitoring Based on CdZnTe Compton Detector for the Accelerator-based Boron Neutron Capture Therapy: The First Experimental Study

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Background and purpose of the study: Boron neutron capture therapy (BNCT) is a binary radiotherapy based on the 10B(n, α)7Li capture reaction. Acquiring the precise distribution of 10B is key to predicting the therapeutic effects in clinical situations [1]. Detecting and reconstructing the 478 keV prompt gamma (PG) ray distribution can be used to estimate therapeutic effect of BNCT. However, the existing scintillator-based measurement equipment is difficult to detect 478 keV PG rays in the complex radiation environment of BNCT due to the poor energy resolution [2]. In contrast, semiconductor detectors (i.e., CdTe, CdZnTe) have attracted significant attention owing to their high stopping power and good energy resolution [3]. This work proposes and demonstrates the feasibility of using a three-dimensional (3D) CdZnTe Compton detector for real-time PG ray distribution monitoring based on the accelerator neutron beam conditions. Materials and Method: Based on the beam conditions of the first accelerator-based

BNCT (AB-BNCT) treatment center in Xiamen, China, an experimental platform based on CdZnTe Compton detector is built. The CdZnTe detector prototype is developed by the Kromek group, and the size of the crystal is 22 × 22 × 15 mm3. The epithermal neutron beam used in the experiment is generated by the reaction of 2.3 MeV, 1 mA proton and lithium target. H3BO3 sample with 20 g is placed at about 50 cm from the beam port, and the CdZnTe detector is placed about 170 cm away from the side of H3BO3sample. The neutron irradiation time of each experiment is 2 minutes. Results: The results show that the gamma energy peaks of 478 keV, 511 keV and 558 keV can be clearly distinguished from the measured PG energy spectrum, which means the CdZnTe Compton detector can realize the accurate discrimination between 478 keV PG ray and background radiation. Under the condition of epithermal neutron beam parameters, the energy resolution of 478 keV PG ray is about 2.59%. Although CdZnTe crystal will react with scattered neutrons to generate 558 keV gamma ray during treatment, the detection of 478 keV PG ray would not be affected because of the excellent energy resolution of CdZnTe. In addition to verifying the detection of 478 keV PG ray from the perspective of energy spectrum, we also realize the reconstruction of the 478 keV PG ray distribution by using Compton reconstruction algorithm based on the data output from the CdZnTe detector. The spatial distribution of 478 keV PG ray reconstructed by the simple back-projection algorithm is basically consistent with the spatial position of H3BO3 sample placed. Conclusions: This work realizes the real-time PG ray distribution detection based on CdZnTe Compton detector under the accelerator neutron beam conditions for the first time. And this work provides a basis for the clinical application of CdZnTe Compton detector to real-time monitoring of boron concentration distribution in the future.

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ID:96 - Capability of FBP, MLEM and OSEM to monitor boron dose using a Compton Camera in Boron Neutron Capture Therapy

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BNCT is a biochemically targeted hadrontherapy for cancer treatment that utilizes the high neutron reactivity of boron-10 in the thermal and epithermal ranges. As the neutron beam enters the body, neutrons in the beam interact with boron atoms in the body, emitting 478 keV prompt gamma rays. In order to exploit the boron dose of BNCT, many researchers are investigating methods to image the distribution of the prompt gamma rays in real time. One proposed method for real time imaging is using a Compton Camera (CC) to detect the 478 keV prompt gamma rays. The spatial distribution of the prompt gamma rays origins, which are indirectly correlated with the boron dose in the patient, can be estimated through tomographic reconstruction techniques. For CC, the collection of cones can be used as the input for the tomographic reconstruction of the origins. Moreover, the analytical method Back Projection (BP) algorithm, the iterative method Maximum Likelihood Expectation Maximization (MLEM) and the Ordered Subset Expectation Maximization (OSEM) algorithm are mainly used to perform the tomographic image reconstruction. In BNCT, the challenges, such as very low counts, incomplete sampling, are faced in the image reconstruction of CC data. Additionally, the quality of the reconstructed images might be impaired by the limited energy resolution and spatial resolution of the detectors. To the best of our knowledge, a comparison between BP, MLEM and OSEM within boron dose monitoring in BNCT using CC data has not been done yet. Considering the higher detection efficiency of single-stage CC than two-stage CC and multiple-stage CC, the single-stage CC was used to detect the 478 keV prompt gamma within realistic BNCT process with Monte Carlo simulation toolkit Geant4. Firstly, the CT scans of a real patient with a brain tumor (sphere around 2 cm diameter) was obtained from the hospital, and the realistic voxelized phantom was established based on the CT scans. Secondly, the simulations of 478 keV prompt gamma imaging within realistic BNCT process was performed using the voxelized phantom. Then the "True events" were selected for reconstruction based on the Compton

kinematics formula. Finally, three different reconstruction algorithms (FBP, MLEM and OSEM) were applied to reconstruct the boron dose distribution images. The details will be shown in the presentation.

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ID:101 - Automatic segmentation of Head & Neck tumours in CT images using an nnUNet to enhance BNCT TPS

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Treatment Planning Systems (TPS) in BNCT [1] are evolving more and more toward a precise and individualized treatment for patients. In this transition Artificial Intelligence (AI), in particular deep learning, can be helpful with the automatic segmentation of the ROIs, in this way it is possible to segment many images without human induced variability. This can be helpful to radiologists since the segmentation process is very slow and on the other hand it could also be helpful to researchers since it gives a tool which can be used to compare multicentric clinical approaches. By these means, it will then be possible to compare different BNCT treatment plans performed on different machines and by different groups. Thus, it will be possible to compare the dosimetry calculated on a given patient independently from the contouring used during the treatment . Inside this framework the AI_MIGHT project aims to study two tumour types commonly treated with BNCT, in particular Head and Neck Tumours (H&N) and Glioblastomas [2,3]. AI_MIGHT will also take into account two imaging modalities: CT images as the gold standard in clinical BNCT and MRI as a future possible method of boron imaging in BNCT. In this work we focus on H&N tumors and CT images. The first step will be the creation of a standardized dataset for CT images of H&N patients, subsequently a neural network (nnUNet) [4] will be trained for the automatic segmentation of tumoral ROIs.

Setting up a system to collect and standardize data is the first step. Online resources provide several datasets of CT scans of H&N cancer, but it is important to select only useful images for the project. In fact, despite the availability of many datasets on the Cancer Imaging Archive [5], the absence of standardization and uniform protocol of images among institutions may hinder the learning of the neural network. Once the dataset was created and standardized, this was used to train the neural network. The neural network used is the nnUNet, a deep learning-based segmentation method that automatically configures itself. With the help of this deep learning technique, the crucial choices for creating a fruitful segmentation pipeline for every given dataset are streamlined and automated, optimizing each training step by finding the optimal parameters for the specific dataset.

Therefore, a method for automatically segmenting ROIs in H&N cancer CT images will be achieved, and it will provide a tool helpful both to physicians and to researchers and applicable to vast datasets improving the analysis time in both cases. The segmented images will be the basis on which the TPS and dosimetry will be calculated. Results of such computational study are presented in this work.

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ID:123 - AI_MIGHT: Artificial Intelligence methods applied to medical images to enhance and personalize BNCT treatment planning

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BNCT clinical application depends on the use of Treatment Planning Systems to evaluate the correct dosimetric informations to treat each tumor and each patient. Enhancing BNCT and creating an even more personalized therapy are objectives relying, among various things, on the continuous improvement of our TPS systems and our imaging capabilities to correctly estimate the 10B concentration in the tumor and in healthy tissue. Currently CT and 18F-BPA PET images are used to detect the Regions of Interest (ROIs) where the 10B containing drug has been accumulated. Moreover, some studies have been conducted and are ongoing on the possibility of using MRI as the standard tool for boron concentration estimation avoiding ionizing radiation before treatment and relying on a single image modality. Independently from the imaging system the segmented images are then used to create the geometry needed by the TPS for the dosimetric calculations. The segmentation of the ROIs is currently performed by a physician and it is a very time consuming task. We propose an automatic segmentation tool based on Deep Neural Networks (DNN) that could be proficient in helping the medical doctors in analyzing a large amount of scans in a shorter time frame and at the same time it could be useful for researchers to test the quality of their imaging systems and/or their new or improved TPS systems on large datasets. The automatic segmentation tool would speed up the TP optimization phase (patient positioning, beam port configuration, irradiation time), usually requiring substantial time. The final TP would be always established with the guide of the physician but this might represent a significant optimization of the TP workflow. The AI_MIGHT project funded by the Italian National Institute for Nuclear Physics (INFN) aims to apply Artificial Intelligence methods to automatically segment images useful for BNCT TPS optimization. In particular DNNs will be used for the segmentation of multiple imaging modalities, thus producing a useful and fast tool to aid physicians and assist researchers interested in improving TPS systems. In particular AI MIGHT is currently focused on tumors of the head and neck region (HN) and brain tumors such as gliomas as reference tumors for BNCT and will take into account both MRI and CT images. Dataset creation for the two tumor types and both imaging modalities is an important step of the project and will use images from public databases such as the Cancer Imaging Archive. First steps of the project have been implemented and results of the image database creation will be presented alongside the first application of a nnUnet on CT images.

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ID:126 - Feature detection algorithms comparison for quantitative neutron capture radiography track detection

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normalsize In the field of cancer therapies, Boron Neutron Capture Therapy is growing. This therapy is based on irradiating, with low energy neutrons, tumour cells loaded with the ^{10}B isotope. The reaction between thermal neutrons and ^{10}B has a much larger cross section than the neutrons and other atoms in biological material. In addition to this, the reaction releases two high-energy particles with ionizing power that can severely damage the cells where the ^{10}B is concentrated. The basic principle is to ensure that the reaction

$$^{10}B + n \rightarrow \alpha +^{7} Li$$

occurs inside the tumour cells.Therefore, to improve the therapy, it is necessary to find a compound which easily conveys Boron into the tumour cells.

Different techniques are used to observe the uptake and diffusion in tissues of such compounds, but a common operation is to count the traces left by the particles on passive nuclear track detectors such as CR39. Digital images are taken of the latter, in which the tracks are visible in the form of structures called blobs. Using algorithms to identify these structures, it is possible to measure the boron concentration in tissue, through a proper calibration. The aim of this work is to identify the most efficient algorithm to perform this task.

Five algorithms are compared with each other; for three of them, Difference of Gaussian, Laplacian of Gaussian and Determinant of Hessian, a brief discussion of the scale-space theory behind them is provided in addition to the results obtained. The other two are a threshold algorithm, which is the reference standard, and a neural network trained for the blob's recognition.

Before being able to observe the action of the algorithms on the images, the latter were analyzed from a structural point of view to identify differences between the objects of interest, the blobs, and the background. In the images captured under the microscope, noise is present that prevents the correct calibration of the algorithms' parameters; the presence of background noise negatively affects the proper functioning of algorithms that rely on scale-space. Therefore, a set of artificial images was created that were structurally consistent with the real ones but without the impurities present in the latter. Using this second set, a first part of data taking was carried out with the aim of setting the correct sensitivity of the three mentioned algorithms. Once the optimal value was found, the real images were analyzed to obtain information on the blobs in the image.

The results of all algorithms studied are compared to each other to determine the most efficient. The conclusion reached is that of all of them, the neural network is the most efficient with an average of 86.0 Such values are to be compared with 74.1

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Biology

ID:21 - Efficacy of integrin targeting novel boron carrier for boron neutron capture therapy in F98 rat glioma bearing brain tumor models

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Background: Boron neutron capture therapy (BNCT) is a particle radiation modality capable of selectively destroying tumor cells. The most commonly used boron carrier for BNCT is boronphenylalanine (BPA). BPA is taken up into the tumor cell via the L-type amino acid transporter (LAT-1). However, there are some BPA-refractory situations. Therefore, a novel boron carrier is expected to improve the therapeutic performance of BNCT. Previously, we reported that Maleimide-functionalized closo-dodecaborate albumin conjugate (MID-AC) is effective for BNCT as a boron-10 carrier in F98 rat glioma bearing brain tumor models. MID-AC is the conjugation of Maleimide-functionalized closo-dodecaborate (MID) and serum albumin, which is already known to be an effective drug delivery system. The main feature of MID-AC is that it can maintain intratumoral boron concentration for a long period of time owing to the accumulation mechanism of serum albumin in tumors. While it has tumor-accumulating properties as a drug delivery system, it has the disadvantage of not having biological target in cellular level. In the present study, integrin αvβ3, which is known to be overexpressed in many cancer cells including high grade gliomas, was applied to the novel boron carrier as the system of biological target, and thus cyclic RGD-functionalized closo-dodecaborate albumin conjugates with maleimide (cRGD-MID-AC) by conjugating cyclic arginine-glycine-aspartate (cyclic RGD: cRGD), a known selective inhibitor of integrin αvβ3, and MID, which conjugates with albumin as well as MID-AC, has been developed. We evaluated the efficacy of BNCT using this novel carrier in F98 rat glioma bearing brain tumor models.

Materials and Methods: F98 rat glioma cells exposed to BPA, cRGD-MID-AC, and cRGD-MID were used for cellular uptake and neutron irradiation experiment. Intracellular boron concentrations and compound biological effectiveness (CBE) of each boron carrier was calculated. F98 rat glioma bearing brain tumor models were used for the biodistribution and neutron irradiation experiment after BPA or cRGD-MID-AC intravenous administration.

Results: Intracellular boron concentrations of BPA and cRGD-MID-AC were increased gradually at all exposed time, and CBE for cRGD-MID-AC was comparable to that for BPA. In cRGD-MID-AC, the boron concentration in the tumor was the highest at 8 hours after intravenous administration and tended to be retained longer at 24 hours. BNCT using cRGD-MID-AC was performed at 2.5 and 8 hours after intravenous administration. In vivo neutron irradiation experiment, statistically difference between Untreated group and BNCT using BPA or cRGD-MID-AC was observed by log-rank test. In addition, long-term survivors, which were not observed in BNCT using BPA groups, were observed only in BNCT using cRGD-MID-AC 8 hours group. These experiments suggest that cRGD-MID-AC has sufficient cell-killing effect and BNCT using cRGD-MID-AC is effective in the experimental F98 rat glioma bearing brain tumor models.

Conclusions: cRGD-MID-AC has been shown to provide a therapeutic effect in BNCT for the experimental F98 rat glioma bearing brain tumor models. The effect of albumin as a drug delivery system

increases blood residence time, and the effect of cRGD as a biological target increases cellular selectivity, which provides more highly selective BNCT against high-grade gliomas than BPA. In addition, it was confirmed that the introduction of cRGD improved its therapeutic efficacy compared to MID-AC. Furthermore, cRGD-MID-AC is attractive because it can be administered intravenously as well as BPA and, as in the case of MID-AC, it is expected to contribute to the flexible application of neutron irradiation and the performance of BNCT by retaining boron in the tumor for a long period of time.
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ID:28 - Exploratory Study to Expand the Indication of Boron Neutron Capture Therapy Based on LAT1 Expression in Tumors

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Introduction: The indication for boron neutron capture therapy in the Japanese insurance system is currently unresectable locally advanced or locally recurrent head and neck cancer. One of the challenges of BNCT research now is to expand indications to various types of tumors. It is desirable to develop a method for predicting the therapeutic effect of this therapy and a guideline for determining whether the therapy is indicated or not. In this study, we focused on the amino acid transporter LAT1 molecule and evaluated the relationship between LAT1 expression in tumor cells and accumulation of the boron drug BPA to determine whether LAT1 expression level in the tumor cells is a useful marker for assessing BPA uptake and evaluating the indication for BNCT in the future.

Methods: We quantitatively evaluated BPA uptake in tumor cells SCC-VII with suppressed and strongly expressed LAT1 using CRISPR/Cas9, and compared it to conditions with LAT1 inhibitors using inductively coupled plasma atomic emission spectroscopy(ICP-AES) and flow cytometry

Results: BPA accumulation in cells with strong LAT1 expression was about 1.5-fold higher than that in the target group, and BPA accumulation in cells with attenuated LAT1 expression was comparable to that in cells with LAT1 inhibitor, confirming that the accumulation of BPA in tumor cells is highly dependent on LAT1 expression in tumor cells.

Conclusion: The degree of LAT1 expression in tumor cells is a useful marker for evaluating the indication for BNCT.
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ID:29 - Bystander effect and immune genes expression in HT29 colon adenocarcinoma cell line with Boron Neutron Capture Therapy.

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Colorectal cancer (CRC) is the third commonly diagnosed cancer in the world (Ferlay 2015). In Argentina, CRC is the second most frequent cancer and also the second in mortality. Treatments for this type of cancer include surgery (local excision or colectomy) for curative or palliative purposes, chemotherapy, immunotherapy and radiotherapy. In regards to radiotherapy, it is usually administered to patients who are in advanced stages of the disease, in combination with the treatments described above. However, the effectiveness of photon irradiation is compromised by the physical characteristics of the photon beam itself, resulting in the need to balance local control of tumor growth with the incidence of side effects in surrounding healthy tissue due to the lateral scattering of the beam (Fitzek M, 1999). Boron Neutron Capture Therapy (BNCT), a particle radiotherapy could offer an alternative to photon beam dose limitation since it concentrates the therapeutic dose in the tumor through the selective concentration of boron compounds in the tumor and neutron irradiation reducing the side effects on healthy organs

during the treatment. Different nuclear medicine centers have used the amino acid boronphenylalanine (10BPA) in clinical trials for high grade gliomas and melanomas (Busse 2003, Aihara 2006) with almost no toxic effects. BNCT would be particularly important when treating large or multiple liver metastases, as the risk of radiation induced liver metastases might be higher with photon based techniques (Pozzi 2012, 2013). However, it is not much known about how BNCT contributes to these evident therapeutic outcomes from the cellular level and the tumor microenvironment. The aim of this work is to study the bystander effect of BNCT in non-irradiated cells on their capacity to proliferate and migrate and start studying the direct effect on the expression of genes related to immune system response in irradiated HT29 colon carcinoma cells.

Methodology HT29 cells incubated with 50 ppm of BPA (BNCT) or without BPA (N) were irradiated with 3 and 8 Gy of neutrons at the RA3 nuclear reactor. After 24 hours or 4 days, the supernatants of the irradiated cells were collected and used as conditioned medium for proliferation (MTT) and migration (wound) assays. Total RNA was extracted from irradiated cells and the expression of immune system related genes was measured (qPCR): galectin-1, IRF and INFbeta.

Results Culture medium from irradiated cells with 8 Gy previously incubated with BPA (BNCT) and collected 24 hours after, induced moderate proliferation of non-irradiated cells. No changes were observed with mediums of other conditions. In contrast, culture medium from irradiated cells with 3 Gy incubated with or without BPA (N and BNCT) reduced or cell migration while the medium from irradiated cells with and without BPA at 8 Gy induced it. In regards to gene expression, galectin 1 (induce apoptosis in CD8 cells) increased 24 hours after 3 Gy of neutron irradiation. No differences were observed at higher doses or in the presence of BPA. In addition, 4 days after irradiation, galectin 1 levels decreased at 3 Gy of neutron alone while at the same dose with BPA, galectin 1 levels increased. There is also an increase of galectin 1 at 8 Gy but this effect seems to decrease when irradiated with 8 Gy of neutron in the presence of boron (BNCT group). IFNbeta (related to inflammatory and memory response) shows a considerable increase when irradiated with 8 Gy with and without BPA (N and BNCT).

Conclusion The presence of BPA during neutron irradiation would be beneficial at higher doses (8 Gy) since these genes have antitumoral effects, galectin 1 inducing CD8 lymphocites to apoptosis and IFNbeta stimulating the adaptive immune response. As bystander effects were not conclusive, more studies are needed to determine whether this effect is pro or antitumoral.

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ID:35 - Formulation and optimization of PLGA nanoparticles for boron neutron capture therapy using Box-Behnken design

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Boron neutron capture therapy (BNCT) is a perspective method for the treatment of oncological diseases. The method of BNCT is based on the absorption of a neutron by a stable 10 isotope with the formation of 7Li and an alpha particle with a high energy sufficient to destroy a tumor cell. However, for successful therapy, the concentration of boron per gram of tumor should be 20 µg. The development of new nanoscale delivery systems will allow achieving the concentration of isotope 10B in tumor cells necessary for irradiation with a neutron flux. The synthesis of new delivery systems is a promising direction for increasing the concentration of drugs in tumor cells. Nanoparticles made from a copolymer of lactic and glycolic acids (PLGA) are promising delivery systems for various types of cancer therapy, including BNCT. Nanoparticles based on PLGA are of interest due to their biocompatibility and biodegradability. Formulation and optimization of the process of obtaining nanoparticles with specified parameters for more effective therapy is a popular task for researchers. Box-Behnken plans make it possible to analyze the obtained data and predict the best parameters for synthesizing particles. For the synthesis of PLGA nanoparticles, cobalt 1,2-dicarbollide was chosen due to the large number of boron atoms in its composition and hydrophilic properties. In this work, according to the plans of Box-Behnken, from the previously compiled matrices and the results obtained from them (nanoparticles), the conditions for obtaining PLGA nanoparticles with cobalt 1,2-dicarbollide with a maximum theoretical total drug content of 1.3% by weight were determined and a minimum average diameter of 64 nm, experiments were

also carried out to optimize the selected conditions. A modified double-emulsion method for the preparation of 1,2-dicarbollide-loaded polymeric nanoparticle were used. The amount of polymer - PLGA, the ratio of the organic phase - chloroform and the concentration of the emulsion stabilizer - polyvinyl alcohol (PVA) varied at different ratios of the active substance (cobalt 1,2-dicarbollide) to the polymer. Box-Behnken plans were used to plot drug loading (DL) and average nanoparticle diameter at different parameters. Analysis of the diagram based on a series of experiments made it possible to determine the optimal conditions for obtaining nanoparticles with a maximum total content of the active substance - 1.3% and the smallest average diameter is 64 nm. The obtained parameters of nanoparticles are optimal for effective BNCT, and further experiments on in vitro and in vivo will make it possible to choose drug administration regimens and doses.
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ID:38 - Novel precision BNCT strategy using a new boron agent

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+F35

Introduction Pancreatic cancer is a cancer with a poor prognosis, with a five-year survival rate of less than 10%. Multidisciplinary treatment centered on surgery for early-stage localized pancreatic cancer is considered important to achieve a radical cure for pancreatic cancer. However, pancreatic cancer with high levels of CA19-9, a major tumor marker for pancreatic cancer, is a high-grade cancer, and in recent years, even if the cancer is localized, the indication for surgery is difficult and treatment is considered to be less effective. Therefore, targeted treatment of pancreatic cancer with high CA19-9 levels and curative treatment, including multidisciplinary treatment including surgery, is important. In this study, we propose a novel pancreatic cancer treatment method by constructing a novel boron drug discovery-based precision BNCT targeting high-grade pancreatic cancer with high CA19-9 levels. Materials & Methods We used The Cancer Genome Atlas (TCGA), a public database of cancer-related gene expression, to search for genes associated with boron drug uptake. In addition, the Cancer Cell Line Encyclopedia (CCLE), a public database of human cancer cell lines, was used to analyze genes in human pancreatic cancer cell lines with high CA19-9 levels. To validate the results, experiments were performed using human CA19-9 high or low pancreatic cancer cell lines, and normal fibroblast cells. Simultaneously, we synthesized a new boron drug targeting glucose transporters. The uptake of the new drug was investigated by intracellular observation over time using cell immunostaining with anti-BSH antibodies, measurement of intracellular boron concentration using ICP-MS and pharmacokinetic evaluation using a single cancer model. Neutron irradiation was performed at the Kyoto University Research Reactor Institute to study the therapeutic effect. Results Cross-carcinoma bioinformatics results using TCGA confirmed that the expression of LAT1, a target for BPA uptake, was lower in pancreatic cancer compared to head and neck cancer and malignant brain tumor that showed therapeutic efficacy with BPA-BNCT. Furthermore, in CCLE, LAT1 expression was low and glucose transporter (GLUT1 and GLUT3) expression was high in the human pancreatic cancer cell line group, especially in the high-grade group with high CA19-9, while low-grade pancreatic cancer with low CA19-9 In the cell lines, there was an inverse correlation of high LAT1 and low GLUT In view of the high expression of GLUT in high-grade pancreatic cancer with high CA19-9, the creation of glucose-bound BSH agents was planned and successfully synthesized, which were used in this study BPA, BSH and Glucose-BSH The intracellular boron concentration of boron agents was evaluated and found that Glucose-BSH uptake was higher and BPA uptake was lower in high-grade pancreatic cancer with high CA19-9 levels. Conversely, the opposite was found in low-grade pancreatic cancers with low CA19-9 levels, similar to the genetic analysis. Next, to mimic the tumor microenvironment in cancer, we assessed uptake in a low glucose environment and found a further increase in Glucose-BSH uptake compared to the normal glucose environment. To confirm the specific uptake of Glucose-BSH via GLUT, GLUT inhibitor treatment completely inhibited uptake. Next, pharmacokinetic results in a pancreatic carcinoma-bearing model confirmed specific and high uptake into pancreatic cancer tissue. Subsequently, neutron irradiation in a nuclear reactor showed a strong tumor growth inhibition effect in the novel boron-based drug group. Conclusion To make the

best use of BNCT, a BNCT research strategy with a multidisciplinary treatment perspective is needed. In this study, the discovery of novel boron agents by Precision BNCT targeting high-grade pancreatic cancer with high CA19-9 levels could be a new step forward in BNCT therapeutic strategies.

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ID:39 - RBE estimation of BNCT based on MK model with optimized parameters

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The radiation field of BNCT is a mixed radiation field, which mainly contains the following particles, neutron, proton, photon, alpha particle, and Li particle. In order to facilitate the calculation of the physical dose, the particle dose of the mixed radiation field is divided into boron dose, nitrogen dose, hydrogen dose and photon dose. In the clinical treatment of BNCT, the accuracy of dose calculation is very important. In order to obtain an accurate biological dose, we need to accurately calculate the relative biological effectiveness (RBE) corresponding to the four doses, which is related to biological endpoints and experimental conditions. The MK model is a biophysical model for calculating ion beam RBE and biologically effective dose based on microdosimetry, and there are many existing ion beam clinical experiences based on this model. In this study, the MK model was used to calculate the RBE of the four doses, and the cell experimental data reported in the paper were selected. In addition, an algorithm was designed to optimize the model parameters to ensure the accuracy of the MK model. After calculation, the lineal energy spectrum and dose distribution corresponding to the four doses were obtained, and the RBE of the four doses was obtained when the biological endpoint was 10% of the cell survival fraction. In addition, this study also obtained the dose depth distribution curves of boronated and non-boronated cells, as well as the corresponding RBE depth distribution curves. In this study, the relatively mature MK model was used to calculate RBE, and the algorithm was designed to optimize the parameters of the MK model, which ensured the accuracy of the calculation results, and provided a certain reference for clinical treatment.

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ID:41 - Targeting M-MDSC enhances the therapeutic effect of BNCT in HNSCC

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Boron neutron capture therapy (BNCT) with the high-LET radiation confined to the boron preferentially accumulated in the tumor revealed high response rates for recurrent HNSCC cancer. However, the risk of recurrence remains after treatment, and it is not uncommon in clinical. Myeloid-derived suppressor cells (MDSC) are heterogeneous and immune-suppressive cells. It consists of two large groups of cells termed polymorphonuclear MDSCs (PMN-MDSC) and monocytic MDSCs (M-MDSC). This cell population has been reported associated with advanced stages and poor prognosis in the peripheral blood of HNSCC patients. This study used 4-NQO to induce a spontaneous murine model and treated tumor-bearing mice with the thermal neutron beam from Tsing Hua Open-pool Reactor (THOR). In this spontaneous murine HNSCC model, the tumor progression was associated with the percentage of circulating M-MDSC. In addition, BNCT slightly prolonged the medium survival than the untreated group, but it leading to a dramatic increasing exchange in circulating M-MDSC. Moreover, this trend is similar to clinical recurrent HNSCC patients. To enhance the therapeutic effect of BNCT, we combined BNCT with PLX-3397, a CSF-1R inhibitor to deplete the soaring MMDSC. This combined therapy displayed an excellent effect than BNCT treatment alone in mice. The result indicates that targeting M-MDSC enhances the therapeutic effect of BNCT in HNSCC.

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ID:50 - BORON BIODISTRIBUTION STUDY FOR BNCT WITH BORIC ACID AND BORONOPHENYLALANINE IN AN ORAL CANCER MODEL

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Introduction: We previously demonstrated the therapeutic potential of BNCT/BPA (boronophenylalanine) and BNCT/GB-10 (sodium decahydrodecaborate) for Oral Cancer in the Hamster Cheek Pouch Model (OCHCPM). The efficacy of BNCT improved when both boron compounds were combined (BPA+GB-10), conceivably due to homogeneous boron uptake in heterogeneous tumors. In addition, we previously performed boron biodistribution studies with BA (Boric Acid) in the OCHCPM. Based on the hypothesis that BA and GB-10 will behave similarly in tissues, the aim of this work was to perform boron biodistribution studies with BA+BPA combined in the OCHCPM to optimize the therapeutic efficacy of BNCT. Materials and Methods: Syrian hamsters bearing exophytic tumors (Squamous Cell Carcinoma) induced by cancerization with Dimethylbenzanthracene (DMBA) were used. Eight administration protocols of BA+BPA were evaluated with different final doses of B (65.5 mg10B/Kg, 50 mg10B/Kg, 36 mg10B/Kg, 31 mg10B/Kg and 15.5 mg10B/Kg) and different proportions of each of the compounds:

1. BA, 50 mg 10B / kg, (injected intravenously - iv) + BPA, 15.5 mg 10B/kg, iv; 2. BA, 34.5 mg 10B/kg, iv + BPA, 31 mg 10B/kg, iv; 3. BA, 10-20 mg 10B/kg, iv + BPA, 45.5-55.5 mg10B/kg, iv; 4. BA, 34.5 mg 10B/kg, iv + BPA, 15.5 mg 10B/kg, iv; 5. BA, 10 mg 10B/kg, iv + BPA, 40 mg 10B/kg, iv; 6. BA, 5 mg 10B/kg, iv + BPA, 31 mg 10B/kg, iv; 7. BA, 15.5 mg 10B/kg, iv + BPA, 15.5 mg 10B/kg, iv; 8. BA, 7.75 mg 10B/kg, iv + BPA, 7.75 mg 10B/kg, iv.

The animals were euthanized 3h after the administration of BA+BPA. Blood, tumor, precancerous tissue, normal tissue, liver, spleen and kidney samples were processed for measurement of absolute boron concentration ([B]) by ICP-OES. Results: The mean [B] for the tested protocols were: 80, 64, 40.4, 57 and 35.2 ppm (tumor); 55, 55.7, 26.7, 41 and 20.6 ppm (precancerous tissue); 55, 45, 26.1, 36.7 and 18.1 ppm (normal tissue), considering the 5 final B concentrations of 65.5, 50, 36, 31 and 15.5 mg10B/Kg, respectively. A preferential uptake of tumor versus precancerous tissue (T/PrT) and normal tissue (T/NT) was observed for all protocols, with values ranging between 1.1 and 1.9 for both ratios. Blood (B) [B] for the 3 protocols with final doses of 65.5 mg 10B/kg decreased from 68 to 23 ppm as the ratio of BA to BPA decreased; the same was observed in the 2 protocols with a final dose of 50 mg 10B/kg, in which blood [B] decreased from 51 to 29 ppm. T/B ratios ranged from 0.9 to 4.2 for all protocols tested. Conclusion: The absolute and relative values of [B] corresponding to the protocols under study support the evaluation of the potential therapeutic effect and associated radiotoxicity of BNCT mediated by BA+BPA at RA-3 in the in vivo OCHCMP model.

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ID:54 - Study Of Microglia In Alzheimer's Disease: Chemical Structure And Modeling Of TREM2

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One of the main causes of Alzheimer's disease is a large accumulation of a protein called beta-amyloid, which later forms into plaques, causing great damage to neurons. The same protein negatively affects the function of microglia, the structure that cleans the blood vessels of the brain of various toxins, thereby protecting our brain from all kinds of pathogens. Too much accumulation of amyloid plaques disrupts microglia and it begins to kill healthy neurons, leading to neurodegeneration and Alzheimer's symptoms. However, there is a possibility that, with genetic modification and BNCT, we can fix microglia and prevent neuronal loss in the brain, targeting each beta-amyloid plaque separately to eliminate their further spread. To do this, we need to modify the structure of the microglial receptor, TREM2. This receptor directs microglia function, so in this article we will look at the molecular compounds of the receptor and possible genetic therapies that can be applied to modify TREM2. In this experiment, I modeled the 3D shape of the Trigger receptor expressed on myeloid cells 2, analyzing its chemical properties. Through this experiment it is hoped to find the best approach to manipulate the work of TREM2 for easier navigation of betaamyloid plaques in the brain for its further treatment through BNCT.
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ID:60 - Lithium neutron capture therapy as a potential melanoma treatment modality.

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Melanoma is the most aggressive, recurrent tumor among the skin malignances with high metastatic rate. New approaches for its treatment are investigating. One of perspective experimental methods is boron neutron capture therapy, which was previously used in clinical trials with boronophenylalanine as boron delivery agent. The main issue of successfully conducted BNCT is high boron concentration in the tumor and relatively low boron accumulation in the surrounding tissues and blood. In this work, the authors propose to use isotope 6Li instead of 10B in Li neutron capture therapy due to Li high neutron absorption cross section. 6Li(n,α)3H reaction results in release of alpha-particle and hydrogen isotope 3H without gamma rays emission. The aim of this study was to evaluate lithium accumulation in tumor, skin, blood, kidney and brain in experimental B16 melanoma mice model and to reveal the potential toxicity after single administration of lithium carbonate in dosages of 300 mg/kg or 400 mg/kg body weight. There were no statistically significant differences in Li accumulation observed between those 2 doses. The highest uptake of Li by tumor tissue was measured 30 min after Li administration in dose of 400 mg/kg and was 22.4 μg/g. Li concentration at this time point was 11.5 and 15.5 μg/g in blood and in skin, respectively. The tumor/blood ratio was 2 and tumor/skin ratio at this time point was 1.5. The Li concentrations in kidneys were relatively high, but there were no morphological changes in kidney sections revealed based on the results of PAS-staining and electron microscopy. Lithium concentrations in all tissues decreased to background values over 7 days after drug administration. Thus single doses of lithium carbonate don't cause acute nephrotoxicity and may be implemented in lithium neutron capture therapy as potential modality for melanoma treatment. Further investigations are needed to determine the effectiveness of neutron irradiation with 6Li containing drug.
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ID:66 - Therapeutic efficacy and radiotoxicity of BNCT employing Oligo-Fucoidan and Glutamine as adjuvants in an experimental model.

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Introduction: Boron Neutron Capture Therapy (BNCT) combines selective tumor uptake of 10B compounds and neutron irradiation. Despite extensive research on borated compounds, only BPA (borophenylalanine) and BSH (sodium borocaptate) have been applied in human clinical studies. A strategy that is being evaluated in the BNCT community is the combined administration of 10B compounds with different uptake mechanisms to improve tumor boron targeting homogeneity and therapeutic efficacy. Radiodermatitis is an expected event in radiation treatment. However, this may limit the dose and therefore the efficacy of the treatment. Oligo-Fucoidan (O-Fuco), a brown seaweed extract, has anti-inflammatory and anticancer activities. Glutamine (GLN) reduced the radio/chemotherapy induced dermatitis in patients and inhibited tumor development in an experimental oral cancer model. Radiation therapies applied to primary tumors can induce immunogenic cell death, which can trigger a cytotoxic immune response against the primary tumor and its metastases. The aim of this study was to evaluate the therapeutic efficacy and radiotoxicity of (BPA+GB-10/Decahydrodecaborate)-BNCT (Comb-BNCT) alone or in combination with O-Fuco or GLN, compared to the standard BPA-BNCT protocol. Also, the systemic immune response expressed in the spleen was evaluated for the Comb-BNCT group alone or in combination with O-Fuco or GLN. Materials and Methods: BDIX rats were injected subcutaneously in the right hind flank with DHD/K12/TRb syngeneic colon cancer cells. Three weeks later, the tumor-bearing legs were treated locally with BNCT at the RA-3 Nuclear Reactor. The thermal neutron fluence at the irradiation position was 4.2 × 1012 n cm−2 for all protocols. a- Comb-BNCT: BPA 31 mg 10B /kg bw + GB-10 34 mg 10B/kg bw, i.v. b- Comb-BNCT+O-Fuco: same as (a) + O-Fuco (200 mg/ml) once a week for 7 weeks, joint oral and topical admin. c- Comb-BNCT+GLN: same as (a) + GLN (40 mg/ml) once a week for 7 weeks, with wet compresses. d- BPA-BNCT: 46.5 mg 10B /kg bw de BPA. e- Sham: same manipulation, no treatment. Results: Boron biodistribution studies showed that boron concentration values were 31 ± 7 ppm in tumor; 31±8 ppm in exposed skin and 32±7 ppm in blood for the combination (BPA+GB-10) while for BPA the values were 27±8 ppm in tumor; 23 ± 6 ppm in exposed skin and 14 ± 4 ppm in blood. The post/pre-BNCT ratio of tumor volume at 7 weeks post treatment was significantly lower for all the groups treated with BNCT vs SHAM (p <0.05). Using the end-point “incidence of tumors that underwent a reduction to 50% of initial tumor volume” to further assess therapeutic response, results were 62% for Comb-BNCT alone, 80% for Comb-BNCT+GLN, 73% for Comb-BNCT+O-Fuco and 30% for BPA-BNCT. The incidence of severe dermatitis at two weeks (when the peak occurs) was 100% for BPA-BNCT while for Comb-BNCT, Comb-BNCT+O-Fuco and Comb-BNCT+GLN it was below 70%, this difference being statistically significant (p 0.05). At the systemic level, an increase in CD8 for Comb-BNCT+GLN vs SHAM p 0.01, and an increase in NK for Comb-BNCT vs SHAM p 0.05 were observed. Conclusion: Comb-BNCT improves therapeutic efficacy and reduces radiotoxicity compared to standard BNCT (BPA-BNCT). A systemic immune response was activated after Comb-BNCT.

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ID:77 - Boron neutron capture therapy as an effective treatment modality against human colorectal adenocarcinoma

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Colorectal cancer ranks 3rd place in prevalence and 2nd in mortality among all the other oncological deceases according to WHO data. Boron neutron capture therapy (BNCT) may be one of treatment options for patients with colon and rectum tumors. The aim of this study was to estimate the effectiveness of boron neutron capture therapy in experimental SW-620 colon adenocarcinoma model in vitro and in vivo. Boronphenylalanine (BPA), sodium borocaptate (BSH) and PEG-liposomes with BSH were used as boron delivery agents. Neutron irradiation was performed at the accelerator based epithermal neutron source at Budker Institute of Nuclear Physics, Novosibirsk. Cell samples were placed in polymethyl

methacrylate phantom under Lithium neutron generating target. The control samples were under the same conditions as the experimental ones but far from the radiation generation site. The results of MTT-test were evaluated 96 hours after irradiation: BNCT with all drugs significantly reduced survival from 85to 90% in comparison with the control. Colony forming assay confitmed the results of MTT: survival fraction decreased significantly and was 14% for BNCT with BPA and liposomal BSH and 11% for BSH. The equivalent dose according to calcuations was 1 Gy-Eq for irradiated cells and 6 Gy-Eq for BNCT groups. SW-620 colon adenocarcinoma growing in SCID mice was irradiated after i.v. injection of 350 mg/kg of BPA, 100 mg/kg of BSH and 100 mg/kg PEGylated liposomes with BSH. The mice were placed radially in a lithium polyethylene container with fixation of the hind with tumor to the center of the container to cover the bodies and to reduce radiation exposure. Calculated equivalent dose in the tumor for BNCT with BPA group was 14.70±5.90 Gy-eq, for BNCT with BSH it was 6.63±0.53 Gy-eq and for BNCT with liposomal BSH was 8.8±3.5 Gy-eq. During the 1st month of observation the tumors slowed down their growth by more than 80% in BNCT with BPA group and more than 70% in BSH and liposomal BSH groups compared to control. Nevertheless, tumors in the BNCT groups continued to grow during 2nd month of observation: inhibition of tumor growth was 66%, 60% and 47% for BNCT with BPA, BSH and liposomes, respectively. Tumor growth in control group was significantly faster and reached maximum level at the end of observation period and was 2.7±1.3 cm^3, despite the fact that half of group were excluded because of ethical reasons. The smallest mean tumor volume was observed in BNCT with BPA group which was 0.9±0.5 cm^3 at the end of observation period. Our results have shown the effectiveness of BNCT at the accelerator-based neutron source on SW-620 colon adenocarcinoma model. Further in vivo experiments are being performed to evaluate different ways of drug administration and irradiation protocols on treatment outcomes.
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ID:80 - A veterinary case report: beagle with mastadenoma and nasal carcinoma treated by twice BNCT

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A female beagle bred in a laboratory animal breeding ground, with multiple spontaneous tumors, was treated by BNCT twice in the Xiamen Humanity Hospital BNCT Center on the NeuPexTM AB-BNCT system developed by Neuboron Medical Group. This paper describes the treatment and reports the status of the beagle post-treatment. The treatment was registered and approved by the Laboratory Animal Center of Fujian Medical University (Fuzhou City, Fujian Province); the post-treatment medical care and follow-up was performed in a veterinary hospital in Xiamen City (Pro Pet Hospital). The beagle was named Daji, which means lucky in Chinese. Daji's exact age is uncertain and is determined to be more than 10 years old by a veterinarian judging by the dental abrasion. Daji was first sent to a veterinary clinic near the university for a biopsy of the giant breast tumors, and then it was confirmed as mastadenoma. Afterward, Daji was brought to an animal imaging laboratory of a CRO (MITRO Ltd., Nanjing City, Jiangsu Province) for a 18F-BPA PET/CT scan. The scan showed a relatively low uptake of 18F-BPA in the breast tumors as expected; however, the scan also showed multiple suspicious lesions in Daji, and one of which had a large volume and presented a higher accumulation of 18F-BPA located in her left nasal cavity. A biopsy confirmed its malignancy and a further IHC analysis is currently ongoing. Daji then travelled to Xiamen and a PK study was performed on her using the continuous infusion method (Ono's method) with NBB-001 (a.k.a. BPA). In addition, a CT sim scan was done for the purpose of TPS. Treatment plan was done by NeuMANTA TPS. Few days later, Daji received her first BNCT irradiation with a dosage of 1,000 mg/kg of NBB-001. The targeted lesion was irradiated using NeuPex at 2.3 MeV and 8 mA for s 45 minutes (planned dose limitation: maximum skin dose at

15 Gy-Eq). It was originally planned to perform the 2nd irradiation 4 weeks apart for the nasal tumor. However, the tumor seemed to seriously affect her smell and taste, which resulted in a refusal of eating 3 days after the 1st irradiation (not attributed to BNCT because there was no mucosal response and the brain as well as body were heavily shielded during irradiation). A nasogastric feeding tube was installed to supply nutrition. As a consequence, an emergent second irradiation was performed 6 days after the first irradiation on the nasal area. Because of the low metabolism of Daji, the 2nd irradiation was conducted at a lower BPA dosage of 883 mg/kg. The 2nd irradiation lasted for 24 minutes (prescribed dose: nasal lesion mean dose at 19 Gy-Eq). After the 2nd irradiation, 24 hours later, Daji was able to eat by herself again; 72 hours later she was able to walk outdoor with her tail up. There was neither mucositis, nor cystitis, nor nephritis (no inflammation in the urinary system), nor skin reaction post irradiations. Neither her eyes had reactions. However, gastrointestinal reaction (mucosanguineous feces and fecal occult blood) was observed two days after the 1st irradiation. The maximum small intestine dose reached 19.14 Gy-Eq in the 1st irradiation. Nonetheless, this is not yet a conclusive acute adverse reaction; future investigation is required. Currently, Daji has been well recovered; the nasal tumor was shrinking while the breast tumor presented an internal narcosis in a FDG PET/CT scan 3 weeks after the 1st irradiation. The FDG PET scan also shows a suspicious inflammation of small intestine; however, FOB was no longer observed a few days after the 2nd irradiation. More details will be shown in the presentation.

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ID:86 - Boron delivery using cerebrospinal fluid (CSF) circulation to brain cells in brain tumor model rats for BNCT Ex vivo imaging of BPA using MALDI mass spectrometry imaging

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Boron neutron capture therapy (BNCT) is a cell selective cancer treatment that involves the use of boron-containing drugs and neutron irradiation. 4-Borono-L-phenylalanine (BPA) is a boron drug widely used in BNCT, for the treatment of malignant melanoma, malignant brain tumors, and recurrent head and neck cancer. BPA is imported into the cells by the L-type amino acid transporter (LAT1) which is slightly expressed at the blood-brain barrier (BBB). Developing an efficient delivery system of BPA to brain tumors is one of the challenges BNCT is currently facing. Recently, our laboratory has been developing a system for boron delivery to brain cells via cerebrospinal fluid (CSF), which we call the "boron CSF administration method". In this study, we examined the BPA biodistribution in the brain of a rat after infusion of BPA via CSF circulation, in order to demonstrate the usefulness of this administration method for brain tumors. CSF is primarily produced by the choroid plexuses and flows from the lateral to the third and fourth ventricles before it enters the subarachnoid space (SAS) surrounding the brain and spinal cord. Finally, CSF drains into the veins via several pathways. The potential of harnessing CSF circulation for drug delivery to deep areas of the brain remains a topic of discussion. For decades, CSF circulation was considered to flow through the brain ventricles and into the SAS, with only the contiguous tissues being exposed. Now, it is recognized that the CSF also flows through the parenchyma via a mechanism referred to as CSF microcirculation. In our previous study, we found that, compared to the intravenous (IV) administration method, the BPA administered to the rats with the CSF administration method tended to accumulate quickly and be excreted smoothly from normal cells. In addition, even though the dose of BPA was quite low, at 1/10 of the dose used in the IV administration method, the CSF administration method resulted in high boron accumulation in tumor cells. The CSF-based method may enable low-dose treatment, and lead to reduced toxicity and costs than the IV administration method. In order to validate these findings, ex-vivo imaging of BPA in thin brain tissue slices of rat brain tumor models was conducted, using matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI). First, we performed a time course study of BPA biodistribution in the brain parenchyma when BPA was administered to the lateral ventricle of the rat models. Secondly, the characteristics of BPA biodistribution in the brain tumors via CSF circulation was compared to that of IV administration. The mass images obtained in our study demonstrated that a significant amount of BPA was localized in tumor

cells after administration via CSF circulation. The difference in BPA color intensity between tumor and normal cells was much clearer on the image at longer time point (160 min) than that of early time point (30 min). Moreover, almost all BPA tends to be excreted from the brain cells to CSF at 60 min after the end of infusion. In the second analysis of the comparison between CSF and IV method, both methods demonstrated that BPA was localized in the invasive margin of the brain tumor and distinguished the border between tumor and normal cells. Besides, the images showed a non-uniform BPA accumulation in the tumor, even within the tumor of 5mm in diameter. In conclusion, the administration method using CSF circulation would be an alternative to the IV-based method in BNCT for patients with brain tumor.

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ID:87 - NEUTRON CAPTURE THERAPY (NCT) AGAINST A NEW TARGET: THE ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, irreversible memory loss, disorientation and language impairment. Following the amyloid-β(Aβ) hypothesis, Aβaccumulation in the human brain is the main responsible of the etiology of AD. Therefore, inhibiting or disrupting the Aβaggregation process could be a promising therapeutic strategy for the prevention and treatment of AD [1]. Curcumin has become a research focus due to its effect of anti-Aβfibrils formation but it has the drawback of a high instability and low bioavailability. The reactivity the β-diketone moiety is one of the causes of this drawback. For these reasons, many efforts have been devoted to the synthesis of Curcumin analogues that can improve molecular stability such as monocarbonyl analogues of Curcumin (MAC), in which a carbonyl group replaces the β-diketone functionality. In this context, we exploited a new class of boronated monocarbonyl analogues of Curcumin (Chimera among them (Fig.1)) in which one aromatic ring is replaced with an ortho-carborane. Other types of carborane-containing compounds have been synthesized such as an analogue of the Pittsburgh compound, generally used for AβPET imaging. Aβ42 peptide has been incubated in physiological condition for 4 days, in order to have Aβaggregates in protofibrillar and fibrillar state [1,3]. Then, the samples were characterized using Congo Red staining, one of the compounds commonly used for detecting Aβaggregates or observed by FESEM microscopy. The affinity of the compounds for the Aβaggregates has been evaluated by a spectrofluorometer competition assay using thioflavin T, a reference compound for Aβaggregates detection. Inhibition constant values, derived by Cheng-Prusoff equation [4], showed that BMACs had the highest affinity. Neutron irradiation has been performed on Aβaggregates samples treated with Chimera and observed by FESEM microscopy. A significant disaggregation effect was observed only in the samples treated with Chimera. The irradiated and non-irradiated Aβsamples without compound have also been analyzed by CR staining to confirm the disaggregation inefficacy of the neutron irradiation. These preliminary studies have shown the disaggregation effect of BNCT on Aβaggregates [2].

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ID:89 - Oligo-Fucoidan enhances BPA-BNCT therapeutic effect on tumors: studies of boron biodistribution/microdistribution and microbiota in the hamster cheek pouch oral cancer model

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Introduction BNCT clinical results for Head and Neck cancer have shown a significant therapeutic efficacy. However, there are opportunities to optimize BNCT for this pathology. We previously demonstrated the therapeutic effect of boronophenylalanine (BPA)/BNCT in the hamster cheek pouch oral cancer model. We showed an enhancement in tumor control (from 67% to 94%) when BPA/BNCT was combined with Oligo-Fucoidan, a sulfated polysaccharide isolated from Laminaria japonica with anticancer and immuno-modulatory properties. In the present study we evaluated the potential mechanisms underlying this effect. Biodistribution and qualitative neutron autoradiography studies were performed to evaluate potential differences in absolute boron uptake and microdistribution induced by Oligo-Fucoidan. Besides, as Oligo-Fucoidan was proved useful to increase beneficial microbiota in the gut, pilot studies on hamster cheek pouch oral microbiota were initiated. Microorganisms may contribute to carcinogenesis, as well as shaping cancer immunosurveillance and response to therapy. Materials and methods Hamsters cancerized employing the 8-week protocol were treated with BPA (15.5 mg 10B/kg, 4 animals) and BPA + Oligo-fucoidan (5 animals, 200 mg/kg, topical administration in the cancerized pouch the day before and coupled to BPA injection). Animals were sacrificed 3h post-BPA. Blood, tumor, precancerous tissue, normal pouch, kidney and liver samples were processed for boron measurements by ICP-OES. For preliminary boron microdistribution studies in tumors +/- Oligo-fucoidan, samples were fixed with liquid nitrogen, sectioned and mounted on polycarbonate nuclear track detector foils. Samples were irradiated with 10 13 n/cm 2 at the RA-3 nuclear reactor and then chemically etched during 4 min. For microbiota studies, sterile swabs were used to collect the samples at T0 (non-cancerized pouch), at 8 and 12 weeks of cancerization (3 animals). Bacterial communities were characterized by sequencing the hypervariable regions V3-V4 of 16S rRNA (metagenome amplicon sequencing). Results Oligo-Fucoidan administration exhibited a slight tendency to increase absolute boron concentration in tumor (28.5±11.9 vs 22.2±6.7 ppm) and precancerous tissue (23.6±7.8 vs 17.6±4.9 ppm) (Student's t Test p<0.05). Previous studies showed that BPA uptake in stroma is significantly lower than in parenchyma. In this study, Oligo-fucoidan altered boron uptake in stroma. We observed stromal areas with higher boron uptake that correlated histologically with areas of dense cellular infiltrate. Boron uptake and microdistribution in tumor parenchyma is qualitatively similar between groups. Taxonomy-based analysis at phylum level showed that microbiota composition and proportion changed during cancerization: at T0, a non-cancerized pouch exhibited Proteobacteria (73.0%), Firmicutes (23.5%) and Bacteroidetes (3.0%). At 8 weeks of cancerization, in precancerous tissue, Firmicutes increased to 98.4% and Actinobacteria appeared (1.6%). At the end of cancerization (12 weeks), the precancerous tissue exhibited Firmicutes (79.0%), Actinobacteria (15.0%) and Protobacteria (6.0%). Bacteria composition in the tumor surface was more diverse than in precancerous tissue surrounding tumors: Firmicutes 85.0%, Bacteroidetes 3.0%, Planctomycetes 3.3%, Proteobacteria 2.6%, Fusobacteria 2.25%, unknown bacteria 3.8%. Conclusions Oligo-Fucoidan could be enhancing BNCT tumor control due to an increase in boron uptake in areas with dense cellular infiltrate in stroma, resulting in a higher absolute boron concentration in tumor. As Oligo-fucoidan has immunomodulatory properties, Oligo-fucoidan could be promoting an immune response, favoring the infiltration of activated T cells in stroma. It is known that immune cells have an increased metabolic state when activated, and this occurs during tumor cell destruction. LAT1 acts as an essential transporter of amino acids for these cells, thus conceivably increasing BPA uptake by these cells. Microbiota also plays a crucial role in the immune response to tumors. Ongoing studies are aimed at evaluating the effect of BNCT, Oligo-Fucoidan and BNCT+Oligo-Fucoidan on the hamster cheek pouch microbiota. Strategies that could select anti-tumor microbiota will surely help to enhance BNCT. Acknowledgments Oligo-Fucoidan was provided by Hi-Q Marine Biotech (Taiwan).

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ID:110 - Evaluation of the effects of Boron Neutron Capture Therapy (BNCT) on proliferation of human keratinocytes in in-vitro epidermal models

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This study aims to investigate the radiobiological effects of BNCT on SkinEthicTM Reconstructed Human Epidermis (RHE) constructs, to understand the effects of the mixed-field radiation on healthy human epidermis.

Boron Neutron Capture Therapy (BNCT) is an innovative method of radiotherapy against cancer, to treat solids tumors that hardly respond to traditional therapies. BNCT needs the previous administration of a compound labelled with boron-10 (10B, non-radioactive) with high selectivity for cancer cells, internalized through LAT1 receptors. This pre-treatment is followed by irradiation with thermal or epithermal neutrons at low energy, thermalized into the tissues.

The neutron beam penetrates into the patient across the skin, depositing dose mainly via boron capture and epithermal neutron scattering in hydrogen. This makes skin a possible limiting tissue for the BNCT treatment. It is thus important to study the dose-effect relation in skin, in order to prescribe the treatment dose in the most safe and efficient way.

The skin substitute SkinEthicTM is an in vitro reconstructed human epidermis model from normal human keratinocytes seeded on an inert polycarbonate filter, grown in a culture medium at the gas-liquid interface. This model was chosen for this work due to its high analogy with the in vivo epidermal tissue: histological, morphological and proliferative, skin irritation, phototoxicity tests confirmed the reliability of the response of the constructs to the different analyses, similar to what observed on the native tissue.

For the purpose of this study, both the percentage of proliferating cells within the individual samples (incorporation assay of Bromo-Deoxy-Uridine, BrdU) and the percentage of positive cells to the expression of the Proliferation-Cell Nuclear Antigen (PCNA) are evaluated. Morphological and immunohistochemical analyses show a progressive degradation of the construct over time and following different doses of neutron radiation.

Same analyses were performed on constructs irradiated with photon radiation, the reference radiation used in conventional radiotherapy, to investigate the effectiveness of BNCT in comparison to gamma radiation. These studies aim at enabling the translation of BNCT dose into photon-equivalent units by producing radiobiological results on the dose-effect relation. The presented results are a preliminary collection of data which helped in understanding the advantages and drawbacks of the model and methods.

The high variability between the different constructs makes it difficult to standardize the results and it would be desirable, in the future, to increase the number of samples to obtain a wide case series for statistically significant analyses.

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ID:117 - 3D bioprinted osteosarcoma model for experimental Boron Neutron Capture Therapy (BNCT) applications: methodological aspects

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Osteosarcoma is the most common primary malignant bone tumor affecting children and adolescents. Despite the introduction of several therapeutic options, the treatment and cure of osteosarcoma still remains an open challenge, due to its infiltrative growth that leads to a high incidence of metastasis and, therefore, to low survival rates. A new therapeutic option is required as an alternative or integrative treatment, for this reason, Boron Neutron Capture Therapy (BNCT) has been investigated. BNCT is an experimental binary radiotherapy based on the irradiation with low energy neutron of neoplastic cells previously enriched with atoms of 10-boron (10B) a non-radioactive stable isotope of boron. This alternative technique selectively destroys neoplastic cells while sparing normal ones. After boron administration, the tumor site is irradiated with low energy neutrons, causing neutron capture reaction in boron. This reaction releases two high linear energy transfer (LET) particles: an alfa (α) particle (4He) and a lithium ion (7Li). Since αparticles have very short pathlengths (5-9 m) comparable to the diameter of a single cell, their destructive effects can be limited to boron containing cells. BNCT studies are usually performed on 2D in vitro models that lack to reproduce pathological tumor tissue organization or in vivo on animals a model that is expensive, time-consuming and has to face the 3R's principles. In recent years, 3D bioprinting has led to rapid progress towards the modelling of pathological tissues. In particular, it is attracting for the engineering of tumor tissues, as it allows to mimic in vitro the tumor microenvironment thus improving the ability in modelling cancer. In this context, the goal of the proposed work is to create 3D in vitro osteosarcoma model for BNCT studies.

The first part of the project was addressed to establish a bioprinting method that would allow to obtain a bioprinted colonized osteosarcoma constructs. The other main object of this work was the set-up of a method for the quantification of the intracellular levels of boron uptaken by the osteosarcoma cells encapsulated into the bioink, in order to assess if this 3D model could be effective for BNCT applications. Rat osteosarcoma cell line (UMR-106) was encapsulated into a sodium alginate-SA 8% and gelatin-GL 4% hydrogel and 3D bioprinted with the Cellink INKREDIBLE+® (Cellink AB) in order to obtain constructs with cells. Two different treatments were tested: constructs printed with cells previously exposed to Boronophenylanine (BPA) (pre-printing treatment) and constructs printed with cells not previously enriched with BPA, but exposed to BPA after their printing (post-printing treatment). The pre-printing treatment was intended to evaluate the gel interference with the 10B quantification. The post-printing one was aimed to verify the gel influence on the intracellular boron uptake and to define a method suitable to remove the residual BPA trapped in the gel matrix at the end of the contact time. 3D bioprinted osteosarcoma constructs should represent an effective alternative model in the context of the 3Rs principle (Replacement, Reduction, Refinement) to reduce the use of animal models. The intracellular boron evaluation is a crucial point for BNCT studies. The method for its quantification in cells within constructs needs to be further refined. Preliminary studies have highlighted several critical issues; however, they were able to provide important information for the development of the method. We expect that by improving the method it will be possible to use this newly 3D osteosarcoma model for BNCT studies.

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ID:119 - Study of the biological response in-vitro to determine the validity of extrapolating the compound-dependent factor from glioblastoma to head and neck cancer in BNCT

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Boron Neutron Capture Therapy (BNCT) treatment planning is based on a weighted dose in which dose components are weighted with different relative biological effectiveness (RBE) factors. The most important for the tumor dose is the compound-dependent factor (CBE) which weights the boron dose. The data currently used in clinical trials comes from the radiobiological experiments performed with brain tumor cells and has been extrapolated to head and neck cancers. The purpose of this work is to study the validity of this assumption. We have analyzed the survival of two different cancer cell lines representative of both types of tumor (A172, a glioblastoma cell line and Cal33, a squamous head and neck cancer cell

line), under thermal neutrons after administration of BPA. The irradiations have been performed at the very pure neutron beam (without gamma contamination) at the PF1b line of the reactor of the Institute Laue-Langevin (ILL) of Grenoble, France, where our group has installed a biological laboratory inside the experimental hall. After the irradiation, clonogenic assays were performed for both cell lines. The results show a similar biological response between the two cell lines. The radiobiological coefficients obtained will be useful not only for the evaluation of the weighted dose but also for the recently proposed formalism of the photon isoeffective dose.
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ID:120 - Study of sulfur compounds as potential coadjuvants in Boron Neutron Capture Therapy

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An isotope of sulfur (33S) has been proposed as a coadjuvant neutron capturer for BNCT, for enhancing the tumor dose at small depths. Although sulfur compounds are well known to play important biological roles, no specific uptake studies are known. The sulfur tumor uptake by means of the essential aminoacids methionine and cysteine is a promising approach, by taking advantage of the enhanced metabolism of tumor cells. In particular methionine marked with 11C is used in cancer PET diagnoses. In this work we have analyzed the uptake of both aminoacids in different tumor and normal cells. First, the toxicity of these compounds at high concentrations in the culture medium has been determined, with the result that they are non-toxic even at concentrations above 1 mg/ml. The uptake has been measured with ICP-AES, finding a higher concentration of sulfur in A375 (melanoma) cells treated with cysteine and in Cal33 (head and neck carcinoma) one treated with methionine. However, the results are of a great uncertainty as the presence of sulfur in the control cells is found to be high, and these aminoacids are also present in the culture medium. Then, in order to enhance the uptake of the external sulfur we have started the study of cells treated with a specific culture medium without methionine and cysteine. We have observed how the concentration of these are reduced, and preliminary results will be shown. This opens the way to a partial replacement of the sulfur contained in organisms with a low-sulfur diet previously to the administration of the external methionine or cysteine.
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ID:121 - Breast cancer cells sensitization by gold nanoparticles in the case of Boron-Neutron Capture Therapy - the impact on cell cycle distribution and gamma-H2AX foci formation

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Introduction Boron-Neutron Capture Therapy (BNCT) is a hadrontherapy which is based on the ability of non-radioactive boron-10 isotope to capture thermal neutrons. The effectiveness is dependent on the cellular uptake of boron-10 compound. In the research, triple-negative type (MDA-MB-231) and luminal type (MCF-7) of breast cancer cell lines were used due to their resistancy for commonly used types of treatment. Moreover, these cancer cells were sensitized by gold nanoparticles in two different sizes: 100nm and 50nm. The main aim of the experiment was to analyze the influence of the sensitization by gold nanoparticles in the case of BNCT on cell cycle distribution and gamma-H2AX foci formation. Another aspect is to enlarge the uptake of boron-10 compound and the effectivness of BNCT method in the case of resistant breast cancer treatment due to the usage of gold nanoparticles. Methods MDA-MB-231 and

MCF-7 cell lines were exposed to neutron irradiation which corresponded to 2-2,5 Gy absorbed dose from MARIA research reactor located in National Centre for Nuclear Research in Świerk, Poland. Neutron irradiation of the cells was performed after appropriate time from adding solutions of gold nanoparticles - GNPs (24h or 4h after incubation with GNPs cells were irradiated). BPA was added 4 hours before irradiation of the cancer cells to each sample which has already contained gold nanoparticles. Cell cycle distribution was analyzed after 24 hours post irradiation by flow cytometry (BD LSR II). Gamma-H2AX assay was also performed by flow cytometry which analyzed the fluorescence signal given by foci formation 24 hours after irradiation. Experiments were carried out in three independent trials. Results The obtained results show that there was significant difference in the case of MDA-MB-231 cell cycle distribution. It was noticeable that cells were blocked in G2 phase of the cell cycle after irradiation. In the samples with addition of gold nanoparticles it was observed more cells in G2 phase blocked than in the samples without them. In the case of MCF-7, there were no samples in which cell cycle was blocked in G2 phase completely. Comparing the results of MDA-MB-231 cell cycle distribution with MCF-7 cell cycle distribution, it was easy to notice that the difference between amount of cells in G1 and G2 phase were quite distinct and MDA-MB-231 cancer cells were better reacting to the usage of gold nanoparticles. However, the addition of gold nanoparticles increased the amount of cells in G2 phase in the case of both types of breast cancer cells. In the gamma-H2AX assay, the fluorescence signal of foci in MDA-MB-231 cancer cells was highly increased in the case of irradiated samples with gold nanoparticles. In the case of MCF-7 cells, the results has shown none significant difference between the fluorescence signal in irradiated and non-irradiated samples. Therefore, in some trials with addition of gold nanoparticles, it could be observed the slight increase in the fluorescence signal of gamma-H2AX post irradiation. Conclusion The results demonstrate that the addition of solution of gold nanoparticles was highly improving the effectiveness of Boron-Neutron Capture Therapy. Therefore, there was observable difference in the results of the effectiveness of BNCT according to the type of cancer cells on which therapy was performed. From this results, it is noticeable that triple-negative type MDA-MB-231 was better reacting for BNCT treatment with gold nanoparticles than luminal type MCF-7. However, the exact cause of such results currently is unknown and there is a need for further research in that topic.
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ID:122 - Survival of human melanoma A375 cells after irradiation with thermal and near-epithermal fast neutron beam.

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The experimental determination of the Relative Biological Effectiveness (RBE) for thermal neutrons is essential for an optimal application of Boron Neutron Capture Therapy. Generally, the RBE related to low energy neutrons and to epithermal neutrons has been considered to be the same. One of the main reasons for this assumption comes from the difficulty to separate the biological effect due to neutrons of different energies after a neutron beam irradiation. However, both effects may be different and, mostly for the epithermal RBE factor, it highly depends on the beam spectrum and flux. Therefore, the common assumption that epithermal and thermal neutron effects are the same may be reconsidered or proven.

The present study compares the survival fraction of the human melanoma A375 cell line, after being irradiated with a pure low-energy neutron beam (at the nuclear reactor of the Institut Laue-Langevin, Grenoble) and with a near-epithermal fast beam (from a TANDEM accelerator and lithium target at CNA Seville, with almost no thermal neutron dose). The experimental arrangement was designed to minimize neutron-induced secondary gamma radiation. In addition, the cells were irradiated with photons at a medical linear accelerator (Hospital Universitario Virgen de las Nieves, Granada), providing reference data for comparison with those obtained from neutron irradiation. Survival of cancer cells after irradiation was studied through clonogenic assays. Preliminary results suggest that epithermal neutrons induce lower biological damage than thermal neutrons. These data show the need to carry out further experiments with the different beams and to get the RBE for each of them separately.
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Chemistry

ID:27 - Development of composite nanomaterials as boron carriers in BNCT

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Inorganic nanoparticles of boron-rich compounds represent an attractive alternative to boron-containing molecules, such as boronophenylalanine or boranes, for BNCT applications. The use of nanoparticles as 10B carriers in BNCT would allow for a high 10B concentration to accumulate in the tumor and for long retention times in the organism. In our study, two different boron-rich inorganic compounds have been investigated: boron carbide (B4C) and boron nitride (BN). Boron carbide presents a high volumetric content of boron and presents remarkable chemical stability, ensuring that no harmful species are released once administered. Hexagonal boron nitride offers a lower volumetric content of boron, but possesses unique properties which arise from the synergic effects of surface chemistry, quantum confinement effects, and the presence of defect centres in its structure. The development of composite nanoparticles, including MRI and optically detectable components, offers the possibility to visualize the distribution of the BNCT active nanoparticles, giving an unprecedented opportunity to control the distribution of the active element before or even during the treatment. Composite NPs were obtained through the co-precipitation of superparamagnetic iron oxides on B4C NPs and the co-localization of B4C and Fe3O4 NPs through the synthesis of Inter polyelectrolyte complexes NPs. Gd-functionalized B4C NPs were also obtained through the precipitation of a Gd-rich solid phase on B4C NPs. The obtained nanomaterials are water stabilized with poly acrylic acid (PAA). A fluorophore (DiI) is included in the PAA shell, allowing the confocal microscopy imaging of the nanoparticles. The obtained nanostructures have been thoroughly characterized by XRD, SEM, TEM, DSC, and μ-FTIR. The interaction and activity of these fluorescent NPs with cultured cells were carried out through confocal light and electronic microscopy correlative analysis (CLEM). This verified the successful uptake of nanomaterials in both HeLa and Jurkat cell lines. Quantification of 10B through neutronic autoradiography in cells treated with NPs confirmed the accumulation of 10B with low cytotoxicity. Intracellular neutronic autoradiography was carried out as well. BN quantum dots were obtained through hydrothermal synthesis. They are water dispersible and exhibit blue fluorescence when irradiated between 300 and 400nm. After thorough characterization by fluorescence spectroscopy and TEM, their interaction with biological systems was evaluated through confocal microscopy, which highlighted the successful internalization of the produced quantum dots. In conclusion, we developed well-characterized, reproducible, and biologically compatible borated and superparamagnetic composite nanoparticles presenting low cell toxicity and capable of enriching tumour tissues with boron concentration that might be high enough to avoid the use of isotopically enriched boron compounds.

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ID:56 - Biocompatible Iron–Boron Nanoparticles Designed for Neutron Capture Therapy Guided by Magnetic Resonance Imaging

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The combination of multiple functions in a single nanoparticle (NP) represents a key advantage of nanomedicine compared to traditional medical approaches. This is well represented by radiotherapy in which the dose of ionizing radiation should be calibrated on sensitizers biodistribution. Ideally, this is possible when the drug acts both as radiation enhancer and imaging contrast agent. Here, an easy, one-step, laser-assisted synthetic procedure is used to generate iron–boron (Fe–B) NPs featuring the set of functions required to assist neutron capture therapy (NCT) with magnetic resonance imaging. The Fe–B NPs exceed by three orders of magnitude the payload of boron isotopes contained in clinical sensitizers. The Fe–B NPs have magnetic properties of interest also for magnetophoretic accumulation in tissues and magnetic hyperthermia to assist drug permeation in tissues. Besides, Fe–B NPs are biocompatible and undergo slow degradation in the lysosomal environment that facilitates in vivo clearance through the liver–spleen–kidneys pathway. Overall, the Fe–B NPs represent a new promising tool for future exploitation in magnetic resonance imaging-guided boron NCT at higher levels of efficacy and tolerability.
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ID:71 - Carborane containing hydrindones as individual pharmacophores for BNCT: synthesis and chemical reactivity

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Carborane clusters provide a wide range of properties valuable for drug design. They have a unique ability for non-covalent interaction, including ionic reactions and the formation of hydrogen bonds, which means carborane derivatives are soluble in water and compatible with various biological fluids. Their reactivity allows for precise regulation of their chemical properties. As the main advantage over previous generations' boron-containing compounds in BNCT, carboranyl-containing compounds provide a high boron content.

In this review, we synthesized hydrindone derivatives of carboranes. The results can be used in organic synthesis for the preparation of new pharmacologically active substances, as well as for their immobilization on magnetic and gold nanocarriers.

As a result of the study, it was found that C-metal derivatives of isopropyl-o-carborane with benzylidene-malonic ether and their derivatives regiospecifically react regardless of the conditions, ratio, and mixing order of the reagents with the formation of a conjugated product — carboranyl-substituted malonic ether. As an objective of the investigation, we considered the reactions with diethyl 2-(3-nitrobenzylidene)malonate and diethyl 2-(4-(dimethylamino) benzylidene)malonate. By cyclization process of the resulting products with a mixture of acetic and hydrobromic acids, the corresponding carboranyl-containing hydrindones were obtained. A good yield of carboranyl-containing hydrindone was synthesized due to the contribution of the dimethylamino group to the reaction, whereas the nitro-group, leads to a lower yield compared to the unsubstituted hydrindone.

The reactions of 3-(isopropyl-o-carboranyl)-hydrindone with various amines (butylamine, methylamine, morpholine, cyclohexylamine, piperidine, pyridine, tert-butylamine, amino acids), alkali metals and their hydroxides were studied. It was discovered that amines with increased basicity generate Schiff bases when they specifically interact with hydrindone derivatives at the carbonyl group, whereas weaker amines, such as aniline and some amino acids, including histidine, lysine, and arginine, do not interact with any derivatives of carboranyl-containing hydrindones. The weaker basic amines, such as morpholine, interact mostly with the acidic proton of the C-H group of 3-(isopropyl-o-carboranyl)-hydrindone, producing salt at a reagent ratio of 1:1.

Further synthesis of the water-soluble potassium salt of 3-(isopropyl-o-carboranyl) hydrindone opened the way for the in vivo tests. Cytotoxicity tests of the obtained compounds were carried out using the

samples of human hepatocarcinoma cells (HepG2) and human fibroblasts. LD50 is around 1 mg/ml for HepG2 and 0.5 mg/ml for human fibroblasts.

Concentrations of hydrindones in tumors and healthy tissues were determined by monitoring laboratory mice with Ehrlich's carcinoma, A549, HepG2, and MCF7. The main criterion for effective cancer therapy, in which the biodistribution of carboranyl-containing compounds in the system "normal tissue:tumor" should not be less than 1:3, was fulfilled. Based on these outcomes, synthesized carboranyl-containing hydrindones may offer a new approach for the development of potential pharmacophores for BNCT and can be a promising asset for further studies.

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ID:82 - Large scale preparation of dodecaborane for synthesis of BNCT drug intermediates

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Due to the unique neutron capture reaction, 10B(1n, 4He)7Li, (produced highly cell toxic of energettic particles and, short fragments distance), boron compounds had become one of the important weapons for the treatment of cancer (boron neutron capture therapy, BNCT)[1]. 10B enriching boron clusters, such as BSH (sodium mercaptoundecahydro-closo-dodecaborate), with high hydrolytic stability and lower toxicity, had became emerging tools for BNCT when modified with some special small molecule functional groups and tumour-targeting agents to improve the permeability and specificity[2]. Therefor, the large scale preparation of closo-dodecaborane dianion, the precursor of BSH, was fascinating. closo-Dodecaborate dianion was a regular icosahedral cage skeleton compound with high stability, high symmetry and three-dimensional aromaticity[3]. There are some methods for preparated dodecaborate, but most of them had defects such as high toxicity, high reaction conditions and low yield[4]. Pyrolysis of boron hydrides to prepare dodecaborate was a relatively facile route. We had prepared dodecaborate convenient by pyrolysis of sodium borohydride and using aryl halide with high boiling point in diglyme at atmospheric pressure. Under reflux and argon atmosphere, aryl halide was dropped into the suspension of NaBH4 in diglyme. After reacted 3 h with stirring, the diglyme was removed by vacuum distillation. The resulting white solid precipitate was dissolved in diluted sulfuric acid and (n-C4H9)4N)Br was added, the precipitate, (n-C4H9)4N)2B12H12, was filtered and dried in air. The yield was 220 g (about 80% calculated by boron) and the production scale could be further expanded. Different from the route of obtaining octahydrotriborate anion by pyrolysis at low-temperature and then increasing the temperature to obtain dodecaborate, this route directly produced dodecaborate by pyrolysis at high-temperature which would improved the yield and purity (tetrahydroborate was produced during the pyrolysis of octahydrotriborate to dodecaborate). The yield of dodecaborate depended strongly on the pyrolysis temperature, increasing the pyrolysis temperature was conducive to the formation of dodecaborane due to the high stability, so the pyrolysis was carried out under diglyme reflux (about 162℃) and the added aryl halide needed to have a high boiling point. [1] Jorgen Carlsson, Stefan Sjoberg and Bengt S. Larsson, Present Status of Boron Neutron Capture Therapy, Acta Oncologica, 1992, 31, 803-813. [2] Manisha Lamba, Avijit Goswami and Anupam Bandyopadhyay, A periodic development of BPA and BSH based derivatives in boron neutron capture therapy (BNCT), Chem. Commun., 2021, 57, 827-839. [3] Martin Lepšík, Martin Srnec, Jaromír Plešek, Miloš Buděšínský, Blanka Klepetářová, Drahomír Hnyk, Bohumír Grüner and Lubomír Rulíšek, Thiocyanation of closo-Dodecaborate B12H122−. A Novel Synthetic Route and Theoretical Elucidation of the Reaction Mechanism, Inorg. Chem., 2010, 49, 5040–5048. [4] Igor B. Sivaev, Vladimir I. Bregadze and Stefan Sjöberg, Chemistry of closo-Dodecaborate Anion [B12H12]2−: A Review, Collect. Czech. Chem. Commun. 2002, 67, 679-727.

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ID:100 - Development of Macrocyclic Polyamine-based Boron Delivery Agents for Neutron Capture Therapy

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Neutron capture therapy (NCT) is one of the unique radiation therapies based on the combination of cancer-specific drugs containing boron-10 (10B) or gadolinium-157 (157Gd) species and the irradiation with thermal neutrons. The neutron capture reactions for the stable isotopes such as 10B and 157Gd produce heavy particles and electrons having destructive effect and short path lengths which limit within single cell diameter. Therefore, cancer cells containing 10B or 157Gd atoms are selectively destroyed with minimum effects on healthy tissues, and hence selective and efficient delivery of NCT drugs into tumor tissue are required for successful NCT. To date, only two boron compounds, disodium mercaptoundecahydrododecaborate (BSH) and L-4-boronophenylalanine (BPA), have been used in clinical NCT for the treatment of cancers including head and neck cancer, glioblastoma, melanoma and so on. Although various NCT agents such as biochemical precursors of nucleic acids, carbohydrates, amino acids, porphyrins, and liposomes are designed and synthesized, most of them do not satisfy the requirement for clinical application. Therefore, the discovery of more potent NCT drugs is highly required for the improvement of NCT. Meanwhile, it is known that polyamines such as spermidine and spermine are essential biomolecules for chromatin structure maintenance, DNA replication and protein synthesis. Besides, intracellular polyamine concentration is increased in cancer cells, therefore several polyamine derivatives have been developed as anti-cancer agents.[1] In previous studies, it was reported that boron-containing polyamines, phenylboronic acid pendant cyclen (cyclen = 1,4,7,10-tetraazacyclododecane), were designed and synthesized as 11B NMR probe for metal ions, and that these molecules are efficiently transferred into cancer cells.[2,3] In this work, therefore, we designed and synthesized novel 10B carriers functionalized with macrocyclic polyamine scaffolds such as [9]aneN3, [12]aneN4, and [15]aneN5 and their Zn2+ complexes, and their cytotoxicity, intracellular uptake and BNCT activities against cancer cells were evaluated.[4,5] The experimental results suggested that metal-free 12- and 15-memberred macrocycles are transferred into cancer cells and their complexes with intracellular metals such as Zn2+ would induce effective cytotoxic effect upon thermal neutron irradiation, possibly via interactions with DNA. In this paper, these results will be reported.

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ID:105 - The first antisense oligonucleotides anti-EGFR decorated with boron clusters (B-ASO) for BNCT

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Nowadays, there is a rapid development of anticancer drugs that can be used against different types of cancer. In this framework, we have developed potential anticancer drugs with dual action. On the one hand, they are antisense oligonucleotides (ASOs) that exert an inhibitory effect on the gene expression of epidermal growth factor receptor (EGFR), a protein that is frequently overexpressed in cancer tissues[1]. On the other hand, these ASOs are conjugated with boron (^{1}0B) clusters, which serve as boron carriers for boron neutron capture therapy (BNCT) aimed at radiologically killing cancerous tissues[2]. In this

way, the developed B-ASOs show potential for effective cancer treatment in cell and animal models[3], 4. Recently, B-ASOs conjugated with N-acetylgalactosamine[5] (GalNAc-B-ASOs) or cholesterol[6] (Chol-B-ASOs) have been developed as targeting ligands. Such decoration ensures transport and selective cellular uptake by specific receptors on tumour cells, while sparing healthy cells.

In this communication, we present the characterization of the studied B-ASOs. Fluorescently labelled (FAM-B-ASOs) are mainly localised in the cytoplasm and decrease EGFR expression via the RNase H activation pathway. Moreover, microscale thermophoresis (MST) analysis confirms the high affinity of the metallacarborane cluster (FESAN) for double-stranded DNA, a property that may improve the efficacy of BNCT [7]. Finally, as demonstrated by inductively coupled plasma mass spectrometry (ICP MS), these GalNAc-B-ASOs and Chol-B-ASOs can effectively penetrate liver (HepG2), glioblastoma (U87- MG), and breast cancer cells (MCF -7), indicating their applicability as boron carriers in BNCT.

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ID:112 - New Boron Analogues of Amino Acid-based Agents for Boron Neutron Capture Therapy

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Following the latest development and popularization of the neutron sources, boron neutron capture therapy (BNCT) has re-attracted great efforts and interest from both academia and pharmaceutical industry. The FDA approved compounds, 4-borono-L-phenylalanine (BPA) and sodium borocaptate (BSH) (Na2B12H11SH), are currently used in clinical trials. Neither BPA nor BSH has fully achieved the tumor selectivity of boron drug for BNCT treatment, preferentially, with its less accumulation in normal tissues and/or blood. Various boron agents have been explored in the last decades with limited individual successes. Nevertheless, it remained a big challenge to develop the boron drug of choice to meet all of the requirements of BNCT. This report summarizes the syntheses of the boron analogues of alpha-amino acid-based agents and their unique efficacy in anti-tumor and anti-rheumatoid arthritis through boron neutron capture therapy. The results suggest that the unprecedented small boron molecules are worthy of further investigation. Acknowledgments: This research was funded by Sunshine Lake Pharma Co. Ltd. References: 1. Zhu, Y.; et al., ACS Omega, 2022, 7, 5864. 2. Zhu, Y.; et al., Chem. Commun. 2021, 57, 10174. 3. Coghi, P.S.; et al., Molecules 2021, 26, 3309. 4. Cai, J.; et al., Molecules, 2020, 25, 4697. 5. Zhu, Y.; et al., Appl. Organomet. Chem. 2020, e5714. 6. Zhu, Y.; et al., Catalysts 2020, 10, 174. 7. Zhu, Y.; et al., Bioorg. Chem. 2019, 90, 103090. 8. Zhu, Y.; et al., Curr. Med. Chem. 2019, 26, 5019 9. Zhu, Y.; ety al., Angew. Chem. Int. Ed. 2018, 57, 14888.

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ID:118 - Selected 10-atom derivatives of mercaptoborate as substrates for the coupling reaction with the neurotransmitter protein

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Cancer diseases are among the diseases of civilization in the 21st century. There are two factors crucial for the successful treatment of the disease, these are the early detectability and the specificity of the applied therapy. We need new compounds for the effective detection and elimination of tumors. BNCT (Boron Neutron Capture Therapy) selectively targeting the tumor cells can be an effective solution to this problem. The precursor of such research was one of the somatostatin analogs called octreotide. The somatostatin receptors have been found on many types of tumors and the therapy with the use of octreotide has already been applied in clinical practice to treat acromegaly and to appease the symptoms connected with tumors of the endocrine gastric-intestinal-pancreatic system. Nevertheless, searching for new carriers of boron-10 is both necessary and important. This research aims to characterize a new carrier for clusters of boron-10 with sauvagine analog. The literature data indicate this type of boron-10 carrier was not applied in this type of research. Sauvagine binds to the CRF typ2a receptor located on pituitary adenomas (ACTH, PRL, GH, TSH-producing), pancreatic tumors such as insulinomas, gastrinomas, central nervous system tumors (neuroblastomas, meningiomas, paragangliomas), prostate, breast and colon cancers. The purpose of this project is the development of a new compound for BNCT to enable the treatment of many types of cancers. Compounds with ten carbon atoms with the exposed sulfone group were selected. Chemical compounds have been studied in terms of biochemistry (lipophilicity, measurement of boron in cell fractions) and cellular response (cytotoxicity, apoptosis, necrosis, serum stability). Due to their structure, 10-atoms clusters of boron are easily coupled with proteins. Additionally, by dint of showing poor EPR signal are detectable in biological structures. These compounds not crossed the cell membrane but internalization to the membrane after four hours. Survivability of the cells correlated with the cytotoxicity of the compounds tested. The apoptosis pathway is contingent on the concentration of the compound tested, not on the incubation period.
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Clinics

ID:51 - Should Canada Join the Preclinical and Clinical Research of Boron Neutron Capture Therapy?

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Purpose/Objectives: Canada recently closed its major neutron source, NRU reactor in Chalk River, that was accessed by a community of about 800 researchers including the late Bertram Brockhouse (Nobel Prize in Physics 1994). A replacement prototype compact accelerator-based neutron source (CANS) has been planned for proposed research in materials development, Small-Angle Neutron Scattering diffractometer, archaeology, and BNCT. We are applying for Canada Foundation for Innovation (CFI) 2023 Innovation Fund (CFI project number: 42891) to develop a low-cost accelerator-based Boron Neutron Capture Therapy (AB-BNCT) in an acute care hospital. However, there is no clear understanding about how Canadian radiation oncologists (RO), medical physicists (MP) and their residents-in-training perceive BNCT and its impact on radiation oncology as a discipline. We conducted a national survey to identify the challenges to build the first BNCT research center in Canada.

Materials/Methods: This survey contains 17 questions in 3 domains: eligibility, demographics, and specific knowledge of BNCT. After REB approval, it is distributed by two national professional organizations, i.e. Canadian Association for Radiation Oncology (CARO) and Canadian Organization of Medical Physicists (COMP). Eligibility is limited to RO with an independent/academic license, board-certified MP, or residents in a formal residency-training program. It is voluntary, anonymous, and without compensation. The results were analyzed using descriptive statistics.

Results: We collected 118 valid responses from all ten provinces: the majority from Ontario (45.7%) and Quebec (18.6%) that have 61% of the Canadian population. There are 70 RO (59.3%) and 48 MP (40.7%), including 7 RO and 2 MP residents. Gender, age group, and years of practice are well representing the current Canadian radiation oncology workforce (e.g. 72% male, 40.7% in age group 35-45 years, and 30.5% had 10-20 year independent practice). Most people know BNCT's indications or rationale (60.2%). However, only 1.4% RO referred, observed, or participated in BNCT, versus 0%, 2.1%, and 2.1% in MP, respectively. Many do not know the reasons of early BNCT's failure (44.1%). Others blame lack of clinical trials and limited neutron sources (42.4%); nuclear reactors not suited to perform clinical procedures (34.7%); no modern treatment planning system (34.7%); lack of precision in measuring boron concentration in vivo (28.8%); no effective boron compounds (24.6%); or presence of undesired radiation in neutron beam (16.9%). Only 29.7%, 8% and 5% correctly identified Japan as the first country to approve routine AB-BNCT for recurrent head and neck cancer in 2020, knew about 20 AB-BNCT facilities globally, and were aware of 20 countries attended IAEA's BNCT meeting to update its technical guidance document on BNCT (IAEA-TECDOC-1223) in 2020, respectively. BNCT was recommended for the 4 common indications by 15.7%-18.6% of RO, i.e. large unresectable glioblastoma multiforme, malignant meningioma, or head and neck cancer that recurred/progressed after maximal dose chemoradiation, or large unresectable localized malignant melanoma that recurred/progressed after multiple surgeries. The majority (87.3%) agreed that Canada definitely should (63.6%) or possibly should (23.7%) join BNCT preclinical/clinical research and 88.1% of RO/MP either definitely would (55.9%) or possibly would (32.2%) refer a cancer patient to a Canadian BNCT center after such facility becomes available.

Conclusions: Most RO/MP agreed that Canada should join BNCT global research and would refer cancer patient to a Canadian BNCT center. However, the limited knowledge that Canadian RO/MP have

about current global BNCT practice and lack of experience remains a challenge. Further educational sessions to promote BNCT research and CFI funding to build the first AB-BNCT facility are needed to realize this innovative cancer treatment in Canada in the near future.
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ID:61 - Interim results of accelerator based BNCT RCT for refractory high-grade meningiomas

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ID:92 - A Flexible Patient Position Method Combined with Treatment Planning System NeuMANTA for BNCT

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Boron neutron capture therapy (BNCT) has the unique advantages of being a novel therapeutic technique that enables biological targeted therapy with cellular-level precision. As the core subsystem of precision radiotherapy, the Treatment Plan System (TPS) is applied to calculate the expected dose distribution and determine appropriate irradiation parameters for optimal treatment results. Besides the planning, treatment safety and effectiveness is mainly decided by the faithful execution of the plan. It is crucial to ensure the patient is positioned at the planned position with correct angles, otherwise the dose delivery will be incorrect. In conventional radiotherapy, the patient does not need to move but the gantry. However, BNCT currently utilizes fixed beam and therefore the patient need to be moved via a movable treatment couch to the designated position and be fixed during the irradiation. In order to perform the automatic and accurate patient position, a complete workflow linked treatment planning system and patient position system is proposed. 1. Calibrated patient position system. The patient position system consists of two main subsystem, robot system and laser system. Robot system consists of a robot with 6 degrees of freedom mounted to the ceiling and a movable couch. Three groups of laser system are located on the left, right and upper wall with fixed distance to collimator center. So the iso-center of the laser system and collimator center could be calibrated and recorded for patient position. The patient position system not only can work individually, but also it can collaborate with specially designed treatment planning system to work together. 2. Specially designed TPS. NeuMANTA (Multifunctional Arithmetic for Neutron Transportation Analysis) is a new generation BNCT-specific TPS developed by Neuboron, which has capability to provides virtual collimator and laser beam for patient position. In NeuMANTA, irradiation position was defined by incident position pi and direction phi and theta. pi is assumed to be the collimator center, phi and theta are defined as the rotational angle of gantry in conventional radiotherapy. Virtual collimator and laser beam could be visualized in 3D view based on the specified irradiation position. 3. Radiographic marker to link patient position system and TPS. Usually, patient position system and TPS works within separate coordinate system and could not build relationship with each other. However, radiographic marker could be shown in both CT images and aligned by laser beam, which make it possible to register the coordinate system in TPS in patient position system. In treatment room, if 3 radiographic markers on patient skin are aligned with the laser system, it is considered as initial position, the registration is completed, and then irradiation position in TPS could be transformed to patient position system and generate control command to move the robot to designed position. A

phantom is used for demonstration of patient position system, and a group of results shows that the patient position system provides an efficient and accurate method to realize the designed irradiation position in NeuMANTA.
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ID:106 - Promoting the use of a common language for specifying and reporting the doses in Boron Neutron Capture Therapy

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The gross tumour volume (GTV), the clinical target volume (CTV), the planning target volume (PTV) and the planning organ at risk volume (PAR) are identified prior to radiotherapy. The ICRU Report 50 recommendations can be applied to conventional radiotherapy but not completely to Boron Neutron Capture Therapy (BNCT). Since the therapeutic dose of BNCT is the boron dose from the biological targeting characteristic attributed to the use of targeting boron carriers (drugs), but GTV cannot correctly reflect the boron dose information by anatomical images. A method to utilize GTV, CTV, PTV and PAR in BNCT will be discussed and recommended: 1. The GTVanatomy is defined according to anatomical medical images, and the GTVB10 is defined based on functional images which reflect the boron-10 uptake within the tumor (e.g., 18F-BPA PET scan). In therapeutic evaluation, the volumetric dose information, which strongly relates to the therapeutic outcome, is GTVB10. 2. The definition of CTV to deal with the potential infiltration of tumor cells at the boundary and deliver additional dose from the radiation beam to cover the margin in conventional radiotherapy. The boron uptake within the margin of the CTV is very poor or none. Therefore, the use of CTV in BNCT may not benefit patient, but could cause confusion in dose calculation, dose contouring and dose delivery. 3. The PTV is applied to compensate the uncertainties arisen from patient positioning, beam delivery setup, organ movement, and so on. Administration of an additional dose to an additional margin, where there are no or less boron-10 atoms, will not contribute to the therapeutic benefits. The concept of PTV, in our work, is applied to the collimator opening size; that is to say, add an additional margin to the collimator opening in order to compensate the uncertainties. 4. The PRV is proposed to reduce the interobserver errors for the contouring, and provides a conservative dose evaluation for organ at risk. If the PRV with a higher boron uptake (e.g., mucosa) is very close to the tumor, or it locates on the path between neutron beam and tumor, the neutron suppression due to the additional boron-10 atoms should be carefully evaluated. Where there is no boron atom, there is no therapeutic boron dose; thus, it is not recommended to prescribe the dose to CTV and PTV, but only calculate their doses for the consideration of a combined therapy with other radiation therapy modality. The dose coverage of tumor parts that do not absorb boron should be obtained by dose painting by a successive boost of conventional radiotherapy or particle therapy. One should never artificially change the boron concentration in the CTV and PTV margins, which will lead to a distortion of dose calculation during neutron transportation.
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ID:107 - A Comparison of Dose Error Effected by SSD and Collimator Apertures Size

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The therapeutic dose of Boron Neutron Capture Therapy (BNCT) is the boron dose. It is delivered to the 'target region' as an integration result of thermal neutrons and boron-10 atoms distributed in the target volume over an irradiation time. Add an additional margin of target region to the collimator could compensate the uncertainties of patient positioning, organ movement, but this compensation may not be effective to the source-to skin distance (SSD) error. The NeuPex AB-BNCT, a neutron source, and NeuMANTA, a treatment planning system, were used in this study. Take the mean tolerated dose of the brain as an irradiation criterion for real brain tumor cases. When The collimator aperture diameter is 14 cm, with a SSD increase of 3mm, 4mm, and 5 mm, the tumor dose error are <2.29%, <3.17%, and <3.81% respectively; When the collimator aperture diameter is 12 cm, with a SSD increase of 3mm, 4mm, and 5 mm, the tumor dose error are <3.00%, <3.57%, and <4.50% respectively; For the case of 10-cm diameter collimator, with a SSD increase of 3mm, 4mm, and 5 mm, the tumor dose error are <3.58%, <3.87%, and <5.43% respectively. The smaller the collimator aperture, the more stringent the error allowed for the SSD. However, a larger collimator aperture will relatively improve the therapeutic ratio (TR, Dbrain,max/Dtumor,min). Take the maximum tolerated dose of the mucosa as an irradiation criterion for HNC cases. When the collimator aperture diameter is 14 cm, with a SSD increase of 3mm, 4mm, and 5 mm, the tumor dose error are <2.96%, <3.84%, and <4.36% respectively; If the collimator aperture diameter is 12 c and a SSD increase of 3mm, 4mm, and 5 mm, the tumor dose error are <3.07%, <4.15%, and <4.98% respectively. Increasing the SSD with the same collimator aperture diameter leads to a higher dose error in HNC than in brain tumors. Since the HNC tumor may be located in the chin or neck and not completely near to the source port, the tolerance for SSD error is therefore lower than in brain tumor case. In brain tumor cases, the TR is relatively improved due to the increased margin; an opposite result is found in HNC cases. The mucosa has a higher boron-10 uptake and CBE value, so the use of a larger collimator aperture is easy to achieve the mucosa maximum tolerated dose and cannot improve the TR (Dmucosa,max/Dtumor,min) of HNC.
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