20th International Congress on Neutron Capture Therapy

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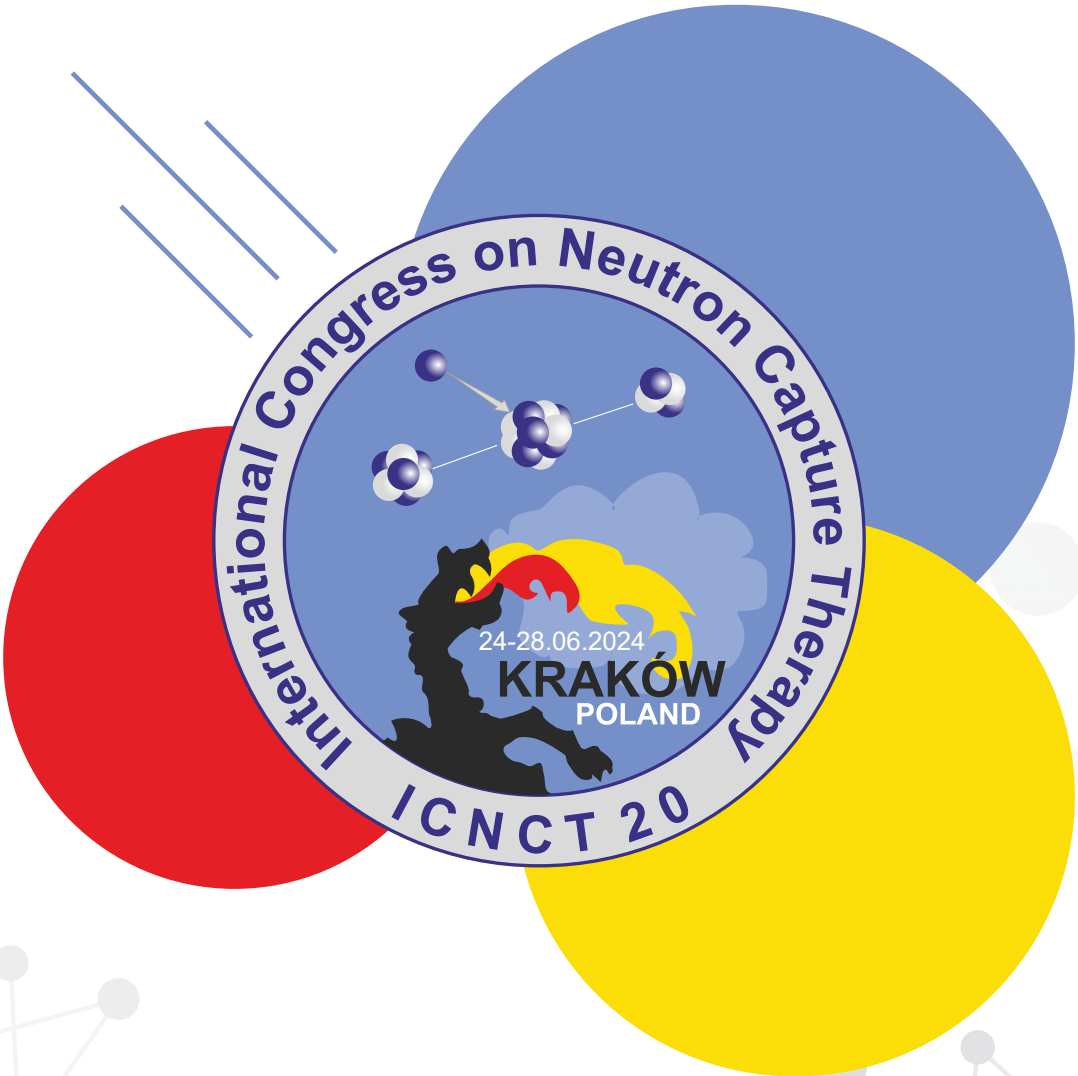

Abstract Book

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PLENARY LECTURES

Plenary 1

Status of BNCT in Poland: clinical, technological and research

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BNCT programme in Poland has started new phase due to three governmental decisions. First concerning finalization neutron beam at MARIA reactor for research, education and training medical personnel. Second supporting 20th ICNCT congress and finally third starting first clinical BNCT facility. Long shut down of reactor MARIA in 2023 enabled to install neutron beam shutter and finally run neutron beam with planned intensity of 10^9 n/cm^2/s. Leading Cancer Centre in Poland (Franciszek Łukaszczyk Oncology Center in Bydgoszcz) announce plans for a New State-of-the-Art BNCT facility. It is projected to complete the centre by 2026, with the first clinical trials scheduled in 2027. Scientific and medical consortium "Polish Consortium for Boron-Neutron Capture Therapy" formed by National Centre for Nuclear Research in 2018 get founds for research and organizing the congress. Now consortium is working on several governmental grants in all aspects starting with neutron dosimetry, synthesis of boron carriers, radiobiology and now also on clinical aspects.
Separate presentation on congress will show progress in research in radiobiology and chemistry: macrofages loaded by boron delivering and depositing boron in the vicinity of tumour tissues, molecularly imprinted polymers in use with BPA, improvements of BSH in radiobiological and diagnostic studies and cellular spheroids as a reference model for BNCT.
In the field of dosimetry, medical physics and physics the consortium will present novel ideas of simple Pg-SPECT based on HPGe detector with reference to recombination ionization detectors and Cr-39 alpha flux determination, on-line system with gel dosimeter combined with laser light acquisition setup and system for QA based on recombination detector and methods (determining four components of the therapeutic dose).
Finally consortium will present technological improvement of intelligent neutron converter for beam intensity modulation and adjustable filter-moderator system for energy spectrum change supporting research in dosimetry systems and radiobiological studies. Those improvements of NCBJ in collaboration with clinical centre in Bydgoszcz started in combining neutron modelling, dosimetry and radiobiology in establish novel treatment planning system.

Keywords: neutron beam, dosimetry, clinical, carriers

Plenary 2

Accelerator neutron sources for BNCT. Where are we now and where might we want to be in 10 years?

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Recent decades have seen the development of accelerator neutron sources suitable for installation in a hospital setting. Numerous challenges have been faced and solved to deliver technology which continues to transform the field of BNCT. This lecture will give an overview of the development of these accelerator technologies and provide a snapshot of the equipment which is currently being used in the clinic.

During this phase of development of accelerator neutron sources there has been scientific debate and now there is some degree of commercial competition on the most appropriate technology and on the quality of the neutron field which is produced from the different technologies. This lecture will pose the question on whether competition on this basis, which may have been important in the early phase of development, will continue to be important. This will be illustrated by some broad comparisons of the published distributions of thermal fluence and epithermal fluence produced by the different available technologies. It will be argued that:
A. these distributions have a high degree of similarity and that,
B. perhaps the debate should shift to comparison and competition on other aspects of the technology, and finally that...
C. such a shift might serve to enhance the perception of BNCT in the wider radiotherapy community

The focus of the lecture will then shift to look at the measures that the physics / accelerator community could prioritise to further drive the development and adoption of BNCT. Here attention will be paid to developments in on-treatment imaging and dose verification technology and the role that accelerator beam design could play in this field. Other aspects which will be important for widespread adoption including the size of facilities and their radioactive inventory will also be highlighted.

Plenary 3

Biofunctionalized boron carbide nanoparticles as targeted boron compounds in boron neutron capture therapy

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Boron neutron capture therapy (BNCT) is based on the nuclear reaction that occurs when boron-10 is irradiated with low-energy thermal neutrons. As a result of this process, the nucleus of the boron-10 isotope is split, which releases energy that destroys cancer cells (1). One of the main challenges for the development of BNCT is the search for selective compounds that provide the required amount of boron in the tumor environment. An interesting aspect is research on nanometric structures such as inorganic nanoparticles as boron carbide or boron nitride. These nanoparticles are characterized by high boron content in their structure. Through targeted synthesis and extensive physicochemical analysis, modification of their surface allows to create the variants specifically targeted to the tumor environment (2). In our research, we modify boron carbide nanoparticles with antibodies, targeted at receptors found in cancer cells, in order to increase the selectivity of their interaction with the tumor environment.
Three cancer cell lines with different levels of expression of low-density lipoprotein receptor (LDLR) and epidermal growth factor receptor (EGFR) on the surface were selected for the study: T98G (glioblastoma multiforme), PC-3 (prostatic adenocarcinoma), SCC-25 (squamous cell carcinoma). The presence of receptors was determined both at the mRNA level using real-time PCR and surface expression using flow cytometry. Cytotoxicity tests of the obtained boron carbide nanoparticles modified on the surface with anti-LDLR and anti-EGFR antibodies were performed on selected cell lines. Then, using flow cytometry and fluorescence microscopy techniques, the interaction of functionalized boron nanoparticles with cells was analyzed.
The results of our research did not show a significant impact of boron carbide surface functionalization on the cytotoxicity of the tested compound. Selected cell lines differed in the level of LDLR and EGFR expression on their surface and the SCC-25 line showed the highest expression level for both receptors. Tests performed with a fluorescence microscope and a flow cytometer confirmed the highest level of interaction of anti-EGFR antibody-modified nanoparticles with the SCC-25 line compared to the other tested cancer cell lines. In conclusion, as a result of the functionalization of boron carbide nanoparticles, stable complexes were obtained showing affinity for cancer cells with a high level of expression of a specific receptor on their surface.
This study was supported by National Science Center, Poland Grant Numbers UMO-2019/33/B/NZ5/02212

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Keywords: boron carbide, BNCT, cancer cells

Progress of accelerator-based boron neutron capture therapy development at Taiwan

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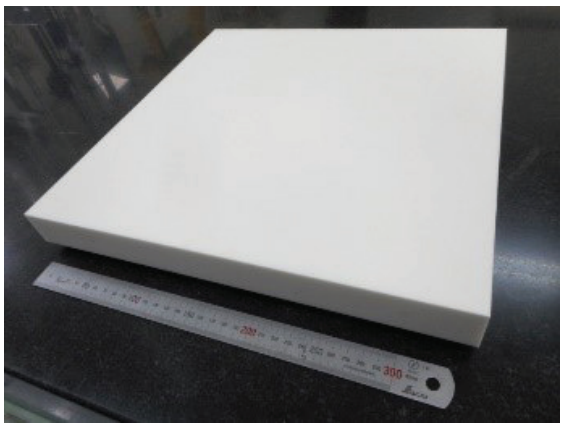

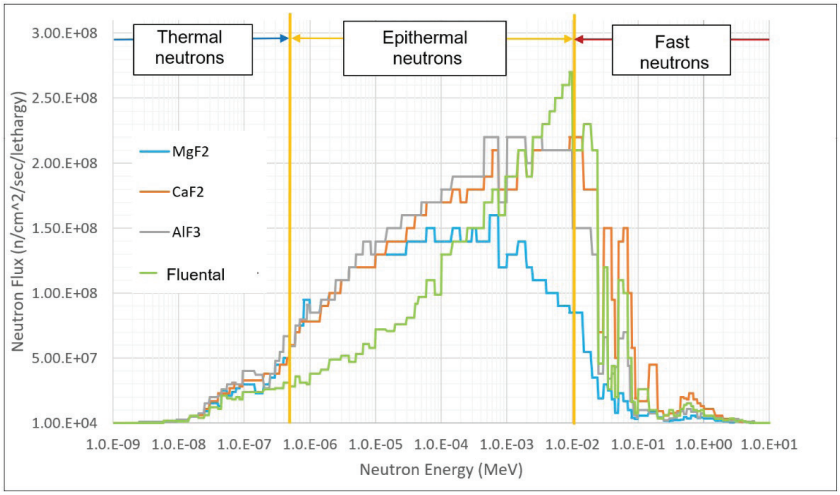

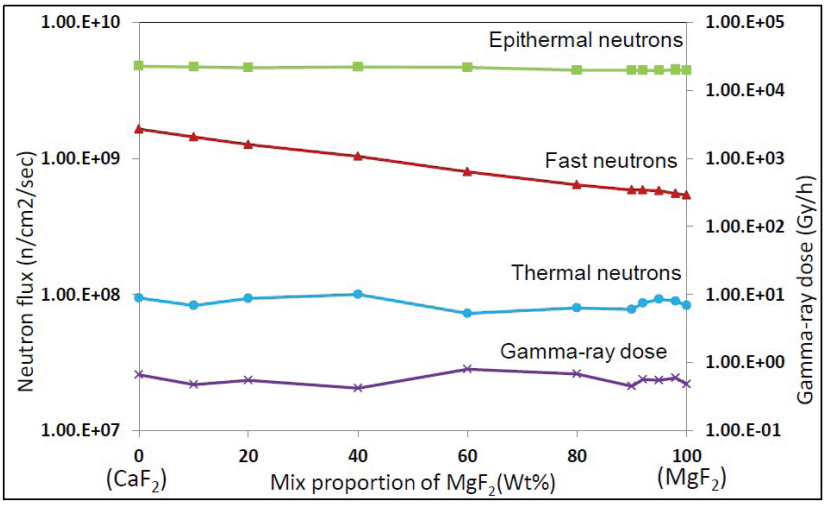

Heron Neutron Medical Corporation has been working on the design and installation for an accelerator-based boron neutron capture therapy (AB-BNCT) facility at Taiwan. The site selection was done on August 2019. The location is nearby the China Medical University hospital at Zhubei. The site construction began in November 2021. The floor area is 35 m by 35 m, an underground two-story-high space.
The AB-BNCT system has two beamlines and two irradiation rooms for an optimal utilization for patient treatment. Other medical area includes boron drug injection room, blood boron analysis room, preparation room and treatment control room. The site planning with shielding design and activation analysis was performed to ensure the radiation safety of the facility outside the concrete bunker for the public and for the working staff. The permission for the construction of this high energy radiation facility was granted in January 2022 by Atomic Energy Council (AEC).
The main magnet of cyclotron was moved-in in November 2022. The building construction was completed in May 2023, followed by installation of cyclotron beamline, and beam shaping assembly. Permission of commissioning was granted by AEC in September 2023. During system commissioning, focus of phase I is on the proton beam testing, including beam diagnosis, measurement of beam current, beam energy, beam profile, integrating of cooling system, safety interlock system, and treatment control system. Focus of Phase II is on neutron beam generation, including installation of target system, neutron beam monitoring system and measurement of neutron beam characteristics. The system shows a good proton beam stability under the future clinical scenario.
At the same time Heron has also been concentrated on providing a total solution for BNCT including the development of BPA and FBPA, followed by pre-clinical test. A series of tests were conducted during the development phase, demonstrating good stability and performance for both drugs.

Keywords: accelerator-based boron neutron capture therapy,

Plenary 5

Tumor response to BNCT and survival outcomes with two boronophenylalanine (BPA) infusion schedules in patients with recurrent squamous cell head and neck carcinoma

Clinical Trials & Routine Practices, Medical Physics

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In boron neutron capture therapy (BNCT) high-LET radiotherapy is achieved by combining external irradiation with low energetic neutrons and a carrier drug that transports ^{10}B selectively into the cancer cells. Single-agent L-boronophenylalanine (L-BPA) has been the most frequently used boron carrier compound. L-BPA has been administrated as intravenous infusion using two different infusion schemes: the L-BPA infusion is either stopped 1 to 2 hours prior to starting neutron irradiation or L-BPA is infused until neutron irradiation and continued during neutron irradiation, but at half of the pre-irradiation infusion rate. In this retrospective study we evaluate patient outcomes after BNCT given with either “the stop scheme” or “the continued L-BPA infusion scheme” in a patient population with inoperable recurrent squamous cell carcinoma of head and neck (rHNSCC). In addition, correlation of the survival and tumor response with parameters tumor size, time from previous radiotherapy and number of BNCT treatments (one or two) was studied. Seventy-nine of the patients (median age 79 years) received neutron irradiation at the FiR 1 research reactor site (Finland) once (49%) or twice (51%), where neutron irradiation was started about 90 minutes after the end of the L-BPA infusion. The L-BPA dose was 400 mg/kg given in 2 hours (rate 200 mg/kg/h). Twenty patients (median age 57 years) were treated at the THOR research reactor (Taiwan) once (45%) or twice (55%), where the cumulative L-BPA dose was the same (400 mg/kg), but the L-BPA infusion rate was slightly slower (180 mg/kg/h), administered over 2 hours before neutron irradiation and continued at the rate of 1.5 mg/kg/min concurrently with neutron irradiation. Median tumor size was 105 cm3 and 20 cm3, for the patients treated in Finland and Taiwan respectively. No difference was found in the response rate (68% vs 60% p=0.49) or survival between the groups treated in Finland or in Taiwan. When survival and response were correlated with the BPA infusion shemae, tumor size, time from previous radiotherapy and number of given BNCT treatments (1 or 2) for entire patient group (n=99), only the small tumor size (p<0.001) was independently associated with longer survival in Cox multivariable regression test. Patients who received two BNCT treatments, reponded more frequently, but did not survive longer. Most patients with rHNSCC to BNCT regardless of time from previous RT and the BPA infusion scheme (continuous or interrupted).

Keywords: BNCT, recurrent SCC, BPA

Plenary 6

A comparative study of the biological response to both BPA administration and neutron irradiation in Head and Neck carcinoma cells versus glioblastoma cells

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Boron Neutron Capture Therapy (BNCT) treatment planning relies on a biological equivalent dose, where dose components are weighted with different relative biological effectiveness (RBE) factors. The primary component for the tumor dose is the compound-dependent factor (CBE), which weights the boron dose. This factor is dependent on the compound used and the tumor type. However, the data currently utilized in clinical trials derive from radiobiological experiments on brain tumor cells and have been extrapolated to different tumor types, as seen in Head and Neck cancers[1]. The main aim of this study was to address the validity of this assumption. Additionally, the DNA damage produced after BNCT is not well understood yet[2,3]. In this work, we have also undertaken the study and comparison of the DNA damage response for both tumor types.
To achieve this, we analyzed the survival of two different cancer cell lines representing both types of tumors (A172, a glioblastoma cell line, and Cal33, a squamous Head and Neck cancer cell line). Both types of cells were irradiated with different doses of thermal neutrons in the presence and absence of BPA. The irradiations were conducted using a very pure neutron beam (without gamma contamination) at the PF1b line of the reactor at the Institut Laue Langevin (ILL) of Grenoble, France, where our group has installed a biological laboratory within the experimental hall. Following the irradiations, the survival rate and the CBE factor were determined for both cell lines through clonogenic assays. Comparisons with the response under photon conventional radiotherapy were performed by irradiating the same cell cultures in the linear accelerator of the University Hospital Virgen de las Nieves (Granada, Spain).
Furthermore, DNA damage studies were conducted at different times (1 h, 6 h and 24 h after irradiation) by evaluating the expression of γH2AX by immunocytochemistry. The results obtained indicate slightly different responses after BNCT between the two cell lines. The CBE factors obtained will be valuable for assessing the weighted dose and optimizing treatment planning in these tumors. Moreover, BNCT resulted in different DNA damage in both cell lines, contributing to a better understanding of the outcomes of this therapy.

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3. Huang CY et al. Boron Neutron Capture Therapy eliminates radioresistant liver cancer cells by targeting DNA damage and repair responses. J Hepatocell Carcinoma. 9, 1385-1401 (2022) Keywords: Head and neck,glioblastoma,BPA,CBE,DNA damage

Plenary 7

Cobaltabis(dicarbollide) [COSAN]-as a boron carrier for BNCT studies in the hamster cheek pouch oral cancer model

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For the advancement of BNCT, the development of new, more selective, non-toxic and effective borated compounds is necessary. Carboranes are in the spotlight, and cobaltabis(dicarbollide) sodium salt (Na[o-COSAN]) is an interesting example due to its high boron content, low toxicity, high uptake by cancer cells, nucleus accumulation in vitro, and its capacity to strongly interact with DNA and proteins. The therapeutic effect of BNCT mediated (Na[o-COSAN]) has been previously demonstrated for glioblastoma in vitro and in vivo and our group evaluated Na[o-COSAN] biodistribution in the hamster cheek pouch oral cancer model. The aim of the present study was to study, for the first time, the therapeutic effect and induced radiotoxicity of BNCT mediated by Na[o-COSAN] in the hamster oral cancer model. This study contributes to the optimization of BNCT and evaluates the potential of this boron compound in BNCT of head and neck cancer. Syrian hamsters (6 to 8 weeks old) were subjected to the classical cancerization protocol, i.e. topical application of the carcinogen dimethyl-1,2-benzanthracene (DMBA) at 0.5% in mineral oil to the right cheek pouch, twice a week for 12 weeks. Tumor bearing animals were treated with BNCT mediated by Na[o-COSAN] (7.5 mg B/kg b.w., n=8). Na[o-COSAN] was injected 3 hours before irradiation based on our previous biodistribution studies. The absolute boron concentration value was 13.2 ppm in tumor and 7.5 ppm in the surrounding precancerous dose limiting tissue (based on our previous studies). Local pouch irradiation was performed at the RA-3 nuclear reactor, prescribing 5 Gy absorbed dose to precancerous tissue. The hamsters were followed weekly, during 4 weeks post-irradiation, assessing clinical signs and body weight. We monitored toxicity induced by BNCT in terms of mucositis in precancerous tissue, employing a 5 grade scale based on mucositis studies in humans and hamsters and BNCT therapeutic effect as the percentage of tumors with partial, complete, total (partial+complete) response and no response in each tumor volume category at the time of irradiation: small (<10 mm^3), medium (≥10<100 mm^3) and large tumors (≥100 mm^3). Cancerized non-irradiated animals, served as controls (n=8). After BNCT mediated by Na[o-COSAN], we observed no clinical signs of toxicity. Regarding mucositis, only 50% of the hamsters exhibited moderate/severe mucositis at 7 – 10 days after BNCT, which reverted to slight mucositis by the end of the follow-up. At 28 days after BNCT, the % of total tumor responses were significantly higher than in the control group (81% vs 26%, $p<0.01$). We also observed that all large tumors exhibited partial remission, while small and medium tumors exhibited complete responses as high as 77% and 42% respectively. In these two categories (small and medium) only around 25% failed to respond. Although biodistribution studies employing Na[o-COSAN] have shown low uptake in the tumor, BNCT mediated by Na[o-COSAN] induced a significant therapeutic effect on tumors, with only half of the animals with mucositis in the precancerous dose limiting tissue. These results reinforce the importance of radiobiological in vivo studies to assess the potential therapeutic effect of a new boron compound and suggest the potential therapeutic value of Na[o-COSAN] for the treatment of head and neck cancer with BNCT. Future studies will be aimed at studying boron microdistribution in the tumor to explain these results.

Keywords: Boron carrier, metallacarborane, cheek pouch

BNCT for Three-Dimensional In Vitro Oral Cancer Model

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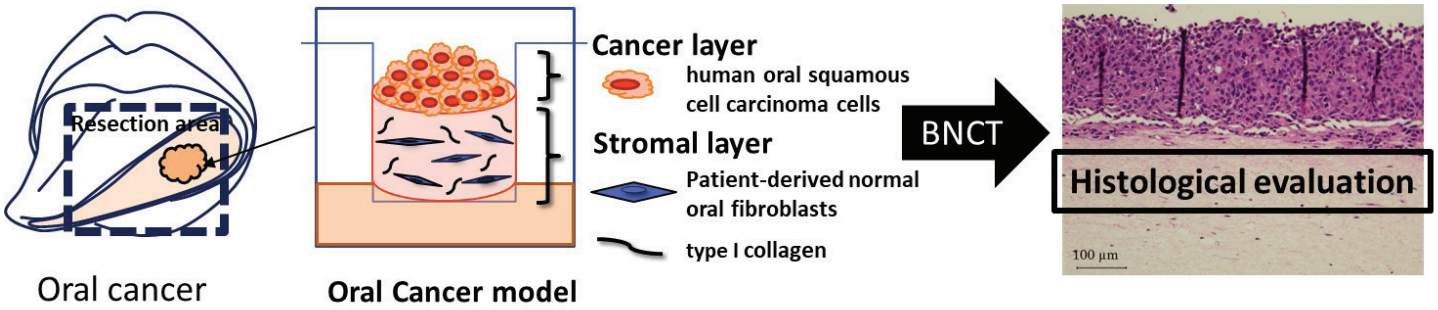

Figure captions: Figure 1 Three-Dimensional In Vitro Oral Cancer Model

Introduction: There are growing expectations for novel radiation therapies to maintain and improve the quality of life of cancer patients as cancer function-preserving therapies. Boron neutron capture therapy (BNCT), one of the novel cancer radiation therapies, is covered by health insurance for head and neck cancer in Japan from 2020, and further development of boron agents and neutron sources and expansion of indications are underway. However, BNCT requires preclinical studies on new boron agents and new accelerator-based BNCT systems to evaluate safety and efficacy, and thus requires a large amount of money and a long time to reach clinical application. In addition, BNCT preclinical studies employing animal models need ethical approvals, in which animal number and welfare are strictly evaluated, as well as from the legal point of view of animal management in radiation-controlled areas. Therefore, there is a strong need for an alternative animal study models in BNCT, which would select the best conditions before testing in animal models, reducing animal number and enhancing animal welfare. In this study, we report on the safety and efficacy of BNCT using an in vitro human 3D cultured oral cancer model.

Materials and Methods: Patient-derived normal oral fibroblasts (NOFs, Niigata University Ethics Committee approval number 2015-5018) were cultured in collagen with a medium of DMEM containing 10% fetal bovine bovine serum at 37°C for 7 days under 5% CO_2 concentration, and then human oral squamous cell carcinoma cells (SAS, JCRB) were seeded onto the collagen surface and cultured for another 14 days to create a three-dimensional oral cancer model. On day 14 of the three-dimensional oral cancer model, boron drug (STEBORONINE, Stellar Pharma) was added for 24 hours, and the boron concentration was measured by inductively coupled plasma mass spectrometry (ICP). Other three-dimensional oral cancer models with boron addition were neutron irradiated (KUR), fixed with 4% paraformaldehyde 6 days after irradiation, and 5-μm-thick paraffin sections were prepared for histological evaluation by Masson trichrome (MT) staining. A saline-added model was used as control.

Results and Discussion: The boron concentration in the three-dimensional oral cancer model was 26 ppm in the cancer cell layer and 5.9 ppm in the stromal cell layer. 6 days after 20 minutes of neutron irradiation, image analysis under a microscope showed that the cancer cell layer grew in the control group, while the cancer cell layer decreased in the BNCT group. Almost no change in the stromal layer was observed in both groups. BNCT on a three-dimensional in vitro model of oral cancer showed tumor shrinkage and little effect on the stromal layer.

Conclusion: In this study, the three-dimensional oral cancer model was shown to have potential as a preclinical alternative to animal studies. Furthermore, the usefulness of this model needs to be evaluated in comparison with animal models and human data.

References:
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Keywords: preclinical study, 3D model,

Clinical trial of A-BNCT for patients with recurrent glioblastoma

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BNCT is a kind of targeted radiation therapy, the patient receives neutron radiation after injected boron containing chemical substance. The neutron reacts with the boron to kill the boron containing tumor cells selectively.
We have started phase 1/2a clinical trial of LINAC based boron neutron capture therapy (BNCT) for patients with recurrent glioblastoma.
The primary endpoint of the phase 1 is the safety and tolerability of BNCT to determine dose-limiting toxicity (DLT) and define the maximum tolerated dose (MTD) in patients with recurred high-grade gliomas. The primary endpoint of the phase 2a trial is to assess 6-month PFS by modified RANO criteria in patients with recurred glioblastomas. Pharmacokinetic characteristics of boron compound, overall survival, objective response rate are assessed as secondary endpoints. 18F-FDOPA imaging was performed to explore its role as an imaging biomarker.
Three patients were treated with A-BNCT as 9 Gy of neutron radiation dose after administration of boron compound of BPA. Brain MRI and FDOPA PET were taken before BNCT and follow-up was conducted for 1, 2 and 4 months after treatment. 500 mg/kg of BPA was used for BNCT, and the irradiation time was determined by measuring the concentration of BPA in the blood immediately before treatment.
After treatment, none of the three patients experienced any serious side effects of grade 3 or higher as CTCAE v5.0 criteria. Hair loss occurred during the follow-up period after BNCT treatment in all three patients.
Gross hematuria occurred in one patient from the evening of the day of BNCT, but improved after 2 days of treatnent. In One patient, the serum amylase level was elevated in a blood test the next day, but immediately returned to normal without any special treatment. One patient complained that his pre-existing speech disturbance was slightly worsening, but it quickly improved without management, In MRI during the follow up, all three patients developed lesions believed to be radiation necrosis 4, 8, and 10 months respectively after treatment, but these are being controlled with Bevacizumab treatment.
We report preliminary short term experience of A-BNCT.

Keywords: glioblastoma, Boron, neutron, radiation therapy

Plenary 10

Profile of miRNAs in small extracellular vesicles released from glioblastoma cells treated by Boron Neutron Capture Therapy

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Boron neutron capture therapy (BNCT) is a tumor cell-selective particle-beam therapy. In BNCT, patients are administered p-boronophenylalanine (BPA), which is selectively taken up by tumor cells via sodium-independent L-type amino acid transporter 1, and the tumor tissue is irradiated with thermal/epithermal neutrons. High-LET α-particles and recoil ^{7}Li are generated by the capture reaction between ^{10}B and thermal neutrons. These particles have a path length of 5-9 μm and selectively kill tumor cells that have uptaken ^{10}B. Small extra cellular vesicles (sEVs) are 50-150 nm vesicles that play important roles in intercellular communication in physiological and pathological conditions [1]. MiRNAs are encapsulated in lipid membranes such as extracellular vesicles in blood and body fluids, exist stably, are taken up by the cells they reach, and act negatively on target genes, performing post-translational modification [2]. In this study, we investigated the biological significance of miRNAs in sEVs released from post-BNCT glioblastoma cells. Glioblastoma U87 MG cells were treated with 25 ppm of BPA in the culture media for 2 hours and irradiated with thermal neutrons in plastic tubes for 70 min. After irradiation, they were plated into dishes and cultured for 3 days in the 5 % CO_2 incubator. Then, sEVs released into the medium were collected by column chromatography, and miRNAs in sEVs were comprehensively investigated using microarrays. An increase in 21 individual miRNAs (ratio>2) and a decrease in 2 individual miRNAs (ratio<0.5) were detected in BNCT cells compared to non-irradiated cells. Up-regulated miRNAs included miR-650, a prognostic marker in malignant glioma [3], miR-3147, which may serve an oncogenic role in vulvar squamous cell cancer [4], miR-4725-3p, which is known to be involved in xanthohumol, a prenylated flavonoid extracted from the hop plant Humulus lupulus L., inhibition of glioma invasion [5], and miR-4270, that is reported to modulate radiation sensitivity in nasopharyngeal squamous carcinoma [6]. Among detected miRNAs, 23 miRNAs were associated with glioma prognosis in Kaplan Meier Survival Analysis of Overall Survival in The Cancer Genome Atlas (TCGA). In these 23 miRNAs, 20 miRNAs were related to worse prognosis (Hazard ratio: HR >1), except three miRNAs (HR <1) according to the database from Cancer MIRNome. These results suggest miRNA in sEVs after BNCT may proceed tumors, modulate radiation resistance, or inhibit invasion and affect the prognosis of glioma. For future study, it is necessary to validate effects of these sEVs on target genes in tumor microenvironment cells. References: [1] Steinbichler TB, et al. Semin Cancer Biol. 2017;44:170-181. [2] Valadi H, et al. Nat Cell Biol. 2007;9:654-9. [3] Sun B, et al. J Neurooncol. 2013;115:375-80. [4] Ho KH, et al. J Neurochem. 2018;146:269-288. [5] Yang XH, Guo F. Mol Med Rep. 2018;17:6397-6404 [6]Hao W, et al. Tohoku J Exp Med. 2021 ;254:63-70.

Keywords: Glioblastoma, microRNA, microarray, small EVs

Plenary 11

Breaking Boundaries in Nanomedicine: Unleashing the Power of Small Amphiphilic Nanomolecules as Carrier-Free Innovators for Multimodal Synergies

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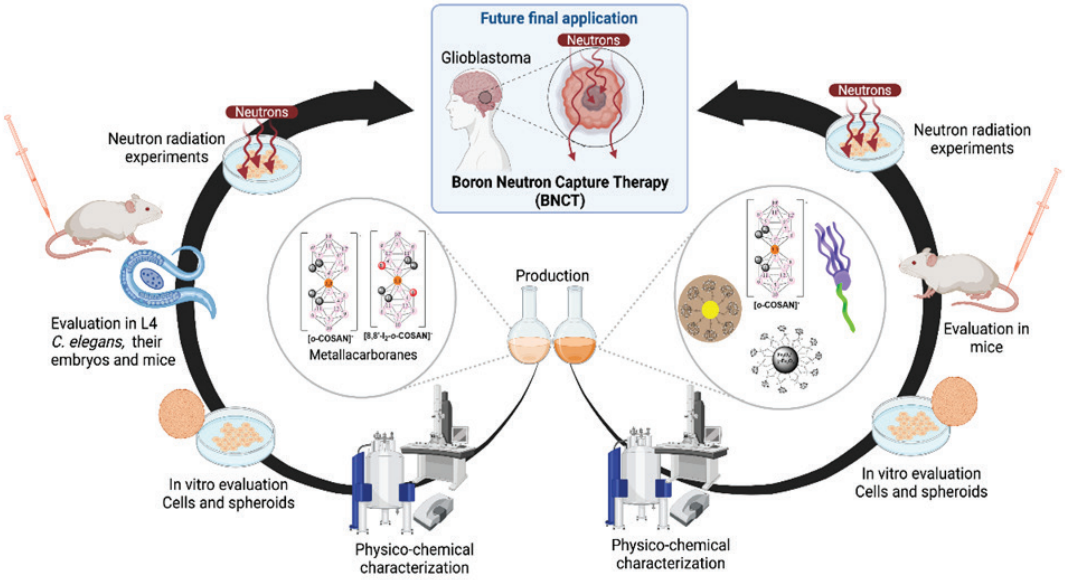

Figure captions: Carboranes and metallabis(dicarbollides) on the road to anticancer therapies: cellular uptake, and in vitro / in vivo biological evaluations to neutron irradiation to defeat cancer.

Aromatic compounds that play important roles in biochemistry found numerous applications from drug delivery to nanotechnology or biological markers. We met an major achievement demonstrating experimentally/theoretically that carboranes (1,2-$C_2B_{10}H_{12}$), as well as anionic cobaltabis(dicarboranes) [3,3'-Co(1,2-$C_2B_9H_{11}$)$_2$]$^-$, display global aromaticity.[1] Based on the relationship between stability-aromaticity, we have opened new applications of boron clusters as key components in the field of new materials for healthcare.[2] Regarding biomedicine, the research has been focused on the development of new nanohybrids (carboranyl + anilinoquinazolines)[3], nanoparticles and, purely inorganic nanovesicles/micelles[4] as vehicles of cancer drugs or as anticancer drugs that, exhibiting desirable in vitro antitumor activities, offer the possibility of dual-action (chemotherapy + BNCT and thermotherapy + BNCT),[3],[5] may result in significant clinical benefits for glioblastoma and breast cancer treatment. Parallel to their use as BNCT agents, boron clusters have been found to be very good scaffolds for diagnostic and therapeutic labelling[6], opening the door to a wide range of biomedical applications. The interaction of metallabis(dicarbollides) with biomolecules (proteins[7], ds-DNA[8] and glucose) as well as their translocation through bilayer membranes were experimentally studied[9]. Molecular dynamic simulations were employed to investigate the translocation mechanism of metallabis(dicarbollide) nano-anions across membranes, which is the result of a flip-flop translocation mechanism with the formation of a transient, elongated structure inside the membrane.
Biodistribution studies of metallacarboranes in (U87) glioblastome and (SKBR-3 and MBA-MB-231) breast cancer cells in xenograft mouse model after 1 and 4 h post i.v. administration showed slow clearance of small metallabis(dicarbollide) molecules in blood and target organs such as heart, liver, lung, kidney, spleen, and muscle but remarkably retention in tumor within a short time. Finally, but not least, taking advantage of their outstanding chemical and biological properties and their retention in tumors we explored the suitability of this small molecules for multimodal (BNCT, PBFT, gamma radiation, X ray, Mössbauer) cancer therapy.

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Keywords: metallacarborane, carborane, 3D-aromaticity, dual-action, nanoparticles,

Plenary 12

Radiobiological concepts and their application in a recently developed Treatment Planning System in BNCT: the application on a glioblastoma in NEMESIS facility. Radiobiological concepts and their application in a recently developed Treatment Planning System in BNCT: the application on a glioblastoma in NEMESIS facility

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A Treatment Planning System (TPS) has been designed for dose-volume estimation of a BNCT treatment from patient's images. The TPS gathers information from patient DICOM images (CT, MRI, and/or PET/CT) and applies geometry and material extraction to the Monte Carlo simulation code MCNP v6.2. A neutron beam, previously modeled from a Monte Carlo code such as MCNP, PHITS or Geant4 can be used as input to the dose engine of the TPS. For the elaboration dose reports, various dose computation models, such as dose-volume histograms and isodose maps, can be used. The TPS helps on the prediction of an optimized BNCT treatment application.
The dependence of the biological damage with the neutron energy is an important aspect that should be included in detail in any tissue damage calculation. Especially in the range of epithermal energies, the dependence of the damage with the beam spectrum can be crucial. However, this fact is not easy to include in the dose estimation, that is why we introduce the concept of Weighted Kerma Factors, an extension of the so-called Kerma Factors that includes the biological effect of each neutron energy. By adding these Weighted Kerma Factors to the MCNP computations, it will be possible to derive the dependence of the damage with the beam straight from the Monte Carlo simulation, cutting down on computation costs and improving damage estimation.
The isoeffective formalism for biological dose calculation as well as the use of the Weighted Kerma Factors has been included in the developed TPS, being capable to predict in detail the outcome of a BNCT treatment on a real patient from its DICOM image and taking into account the influence of the beam spectrum on this damage. The beam corresponding to the Spanish projected BNCT facility (NEMESIS)[1,2] was applied to a glioblastoma case in order to compare with previous results and to search for the optimized conditions for a treatment application.

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Keywords: Treatment Planning, Radiobiology, Dosimetry,

A retrospective study of factors causing grade 3 oral mucositis for locally recurrent inoperable head and neck patients treated with BNCT research reactor in Finland

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A total of 139 patients with head and neck cancer were treated at the FiR 1 research reactor with Boron Neutron Capture Therapy (BNCT) in 1999 to 2012 (1). Patients received 2 hour intravenous L-boronophenylalanine-fructose (L-BPA-F) infusion. The L-BPA dose used was 400 mg/kg. Neutron irradiation was started approximately 1-2 hours after the end of the L-BPA infusion. Patients received 1 to 2 BNCT treatments. There where approximately 4 weeks between the BNCT treatments. In safety and efficacy studies oral mucositis was the most common side effect. 54% of the trial patients had grade 3 mucositis (2). Severe mucositis was the most common reason why the second BNCT was delayed or postponed. In our previous analysis, we found that the maximum physical absorbed dose to the mucosa, biologically weighted mucosa dose with RBE and CBE factors, age, gender, tumor location or tumor histology do not seem to correlate with mucosal toxicity. Our preliminary study suggested that the photon iso-effective dose model may predict mucosal toxicity after BNCT better than the RBE model or physical absorbed doses (3). In this study, we retrospectively evaluate other factors that may have been related to grade 3 oral mucositis in head and neck cancer patients treated with BNCT in FIR 1 research reactor. We evaluate 93 patients with locally recurrent inoperable head and neck cancer. 75 patients had histology of squamous cell cancer, and 18 patients had other histology (adenoid cystic carcinoma, sarcoma, ductal carcinoma, neuroblastoma and adenocarcinoma). We evaluate whether BNCT irradiation time, time from the beginning of L-BPA infusion to the end of irradiation and blood boron concentration were correlated with mucosal toxicity. The BNCT treatments with accelerator based BNCT are going to start in near future in Helsinki. Understanding the relationship between the treatment and occurrence of mucositis will help us to improve BNCT treatments.

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Keywords: BNCT, mucositis, toxicity

Development of a comprehensive skin model for studying the dose-effect relationship using BNCT

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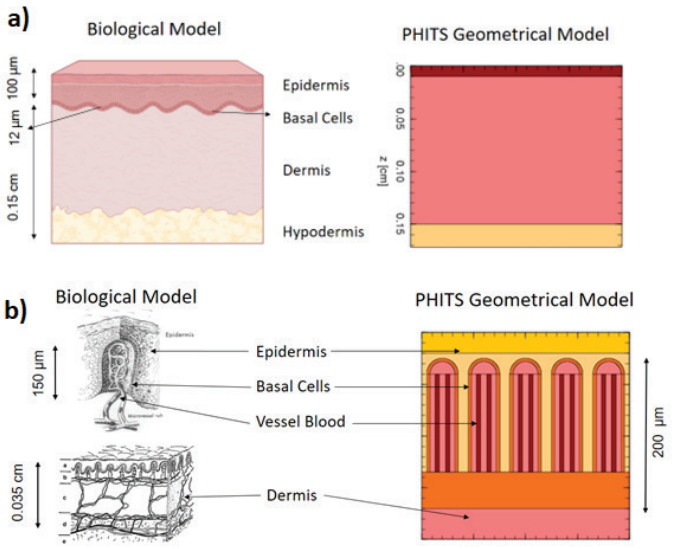

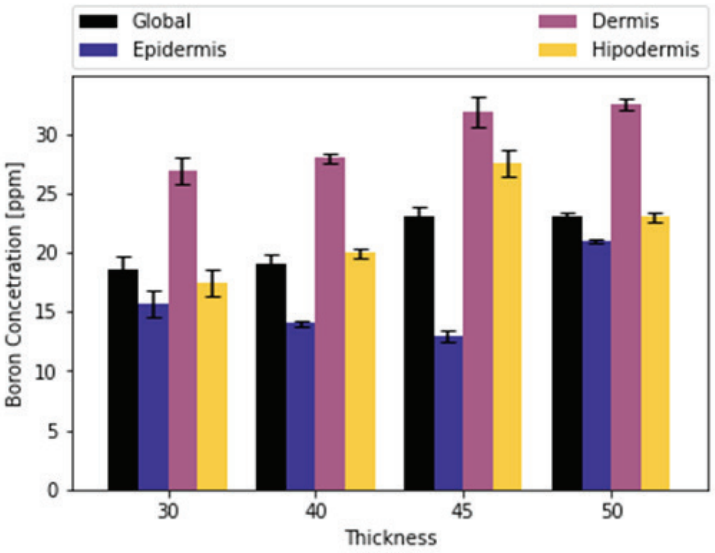

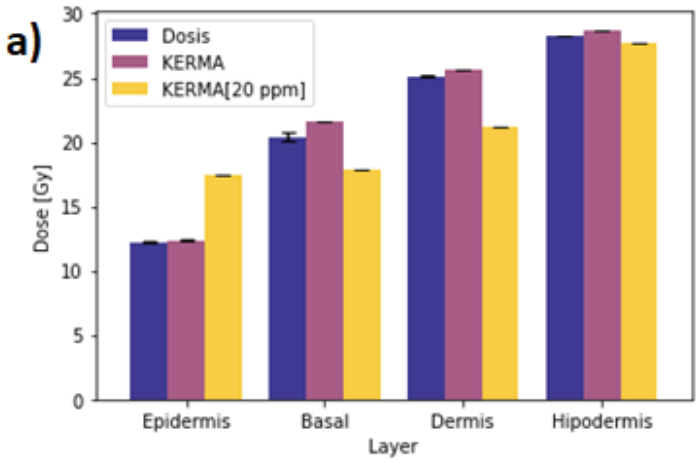

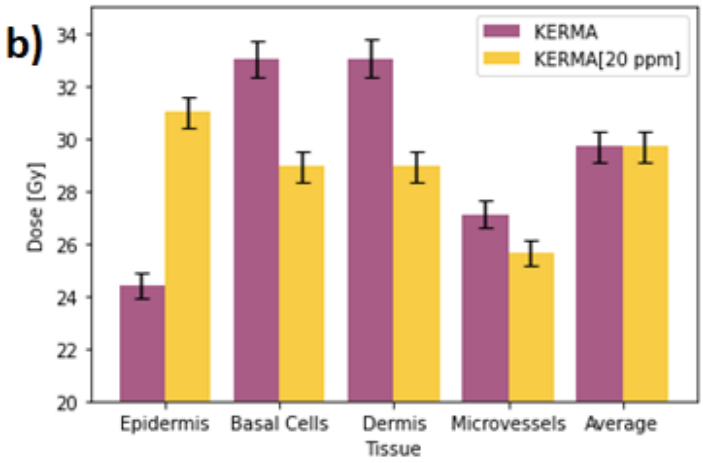

Figure captions:
1: Skin Model. a) Milimeter scale. b) Micrometer scale.
2: Boron uptake in skin layers
3: (a) RBE Dose in skin structrues at millimeter scale. (b) RBE Dose in skin structures at the micrometer scale.

In 2003, a clinical trial was approved in Argentina for the treatment of skin cancer in the extremities using BNCT. Fifteen irradiations were conducted at the BNCT clinical facility of the RA-6 reactor at the Bariloche Atomic Center [1]. Due to its extensive nature and location in the body, the skin is an organ that exhibits a complex response in most radiotherapies, limiting the irradiation time. The main purpose of this work is to address the calculation of detailed dosimetry in the normal skin, aiming to optimize BNCT treatments, and to understand the relationship between radiation dose and quality and possible acute and late toxicities.
Dose calculation models in BNCT usually assume Charged Particle Equilibrium (CPE). Under CPE conditions, the absorbed dose equals the Kinetic Energy Released in Materials (KERMA) of uncharged particles. Hence, it suffices to compute the primary uncharged particle fluxes to determine the administered dose in tissues. In certain conditions involved in BNCT, CPE is not fulfilled due to the lack of a homogeneous distribution of charged particle sources. In such cases, it becomes essential to estimate the dose through more complex calculations.
This work addresses the detailed dosimetry in normal skin through both computational and experimental approaches. Two skin models were taken into consideration. At the millimeter scale (Fig.1a), the tissue comprises three main layers: epidermis, dermis and hypodermis. On the micrometer scale (Fig.1b), additional structures become apparent, such as blood vessels and a 10 µm-thick layer consisting of a single row of cells known as the basal layer.

The computational approach involved simulations using PHITS. For these simulations, skin geometrical models were developed for both spatial scales. The construction of these models involved a comprehensive study of the anatomy and histology of human skin, its different material compositions [2] and thicknesses [3], and the distribution of B-10 in the structures. Dose estimates for the different skin structures were obtained by calculating KERMA and absorbed doses. For the latter, the transport of the main secondary charged particles in BNCT was carried out. Physical doses were converted to doses in photon-equivalent units using the fixed-RBE dose RBE/CBE values typically used for skin were applied for these calculations. In the skin model covering the millimeter scale, KERMA and absorbed doses in Gy (RBE) units were compared, taking into account the B-10 uptake by each layer. Additionally, the estimation of KERMA in each skin layer was included for an average value of B-10 (20 ppm), representing the clinical scenario where a homogeneous concentration of boron is assumed for all layers. In the micrometer-scale model, KERMA values were compared for both homogeneous and heterogeneous distributions.
The experimental approach involved the use of the neutron autoradiography technique [4] to estimate the uptake of boron in different skin structures. Using neutron autoradiography, 21 biological skin samples from a pre-clinical study in a large animal were analyzed. The samples measured approximately one square centimeter and exhibited thicknesses ranging from 30 to 50 microns. They were generated with a microtome at -19°C. Using the optical density formalism, which spatially correlates the distribution of B-10 with the grayscale level of autoradiography, the average concentration of boron in each layer of the skin was determined.
Experimental results showed that the layer where the basal cells are located absorbs a higher concentration of B-10 compared to the average value (Fig.2). According to simulations, this layer would receive approximately 4 Gy (RBE) more than the value obtained for the average boron concentration, representing a 15% increase compared to the clinical scenario (Fig.3). This difference could potentially explain the occurrence of radiotoxic effects during treatments.

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Keywords: Skin, Dose effect, Cancer, Model

Plenary 16

BNCT may preserve neurological function and be an effective approach for metastatic spinal tumor

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[Background] Boron neutron capture therapy (BNCT) is a particle beam therapy that enables precise targeting of tumors at the cellular level. Drawing on the success observed in nuclear reactors, BNCT holds promise as a therapeutic approach for addressing invasive brain tumors, such as malignant gliomas and high-grade meningiomas. While metastatic spinal tumors have been treated by surgical removal, radiation therapy, and various multidisciplinary interventions, none have proven successful in overcoming this metastatic disease. This study aimed to evaluate the efficacy of BNCT in treating metastatic spinal tumor using a mouse model.
[Methods] In the in vitro experiment, neutron irradiation was applied to A549 human lung carcinoma cells with (BNCT group) or without p-boronophenylalanine (BPA) 10 μg Boron/ml for a 24-hour exposure before irradiation (hot control group) for 0, 10, 20 and 30 minutes. The cell-killing effect was assessed using colony forming assay. In the in vivo experiment, A549 subcutaneous tumors were removed and implanted into the lumbar lamina, where they were partially resected. After 4-5 weeks, metastatic spinal tumor model was successfully established. For boron biodistribution, after 2.5, 6, or 24 hours of intravenous BPA administration (250mg/mouse body weight), the tumor bearing animals were euthanized, and the boron concentration of the tumor and each organ was measured using Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES). For in vivo BNCT studies, tumor-bearing mice were randomly assigned to cold control group (untreated, n = 10), hot control group (neutron irradiated only, n = 9), and BNCT group (BPA administration followed by neutron irradiation, n = 10). Survival analysis was conducted using Kaplan-Meier curve. Moreover, neurological function was assessed by Basso-Beattle-Bresnahan (BBB) score. The BBB score is graded 21 (normal function) to 0 (complete paraplegia).
[Results] In the in vitro neutron experiment, BNCT group demonstrated a greater cell-killing effect than the hot control group. The highest boron accumulation in the tumor was observed at 2.5 hours after BPA administration (10.5 μg B/g). Tumor to normal spinal cord ratio (T/N) was 3.6 and tumor to blood ratio (T/Bl) was 2.9. For in vivo BNCT studies showed that BNCT group had significantly prolonged the overall survival compared to the cold control group. In addition, BNCT group had significantly greater BBB score than cold and hot control groups.
[Conclusions] These findings suggest that BNCT may represents a novel and effective approach in the management of metastatic spinal tumor. We believe that we have presented important findings as the first step toward clinical application of BNCT for metastatic spinal tumor.

Keywords: Boron Neutron Capture Therapy (BNCT)

BORON NEUTRON CAPTURE THERAPY EFFECT ON ORAL MICROBIOTA AND ITS POTENTIAL MODULATION WITH THE PREBIOTIC OLIGO-FUCOIDAN: IN VIVO STUDIES IN AN ORAL CANCER EXPERIMENTAL MODEL

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One of the most common types of head and neck tumors is the oral squamous cell carcinoma (OSCC). Many patients develop OSCC without being exposed to the typically reported risk factors. Oral microbiota is a heterogeneous group of microbial species colonizing the surfaces of the oral cavity, and has been associated with OSCC. Microbiota has been included as one of the hallmarks of cancer, as it may contribute to carcinogenesis, metastasis, response to therapy and even the induced toxicity. Different factors can alter oral microbiota proportion and composition and, if this alteration increases the abundance of pathogen species or reduces the beneficial ones, this could initiate disease. One of these factors could be cancer therapy. Oral microbiota richness negatively correlates with radiation doses in head and neck cancer patients. Radiation-induced hyposalivation could shift microbial population toward a pathogenic flora, which could enhance mucositis and tumorigenesis. Prebiotics, biological nutrients that are degraded by microbiota, could help to mitigate these effects. One example is Oligo-Fucoidan, isolated from Laminaria japonica brown seaweed that has been shown to stimulate beneficial bacteria in the gut. Moreover, our group demonstrated an enhancement in tumor control when BNCT was combined with Oligo-Fucoidan in the oral cancer hamster cheek pouch model. This model has been demonstrated to be useful for the study of oral cancer development, treatment and oral microbiota (at phylum level). Within this context, the aim of this study was to evaluate microbiota composition and proportion in normal and cancerized hamsters and if Oligo-Fucoidan and/or BNCT are capable of changing microbiota composition and proportion in tumor-bearing hamsters. Hamsters 6-8 weeks old were cancerized with dimethylbenzanthracene twice a week for 12 weeks. We took samples of microbiota from the tumor, precancerous surrounding tissue and normal tissue in different experimental groups: (A) Pre cancerization (normal pouches) and once the animals have finished the cancerization process; (B) Tumor bearing animals pre Oligo-Fucoidan and after two weeks of Oligo-Fucoidan (200 mg/kg/day, topical application); (C) Cancerized animals with tumors treated with BNCT +/- Oligo-Fucoidan: pre irradiation, and 2 h, 24 h, 10 days, 14 days, and 28 days post treatment. In (C), animals were injected with BPA (15.5 mg B/kg – 3 h before irradiation) and were irradiated at the RA-3 nuclear reactor (Buenos Aires) at 2.6 Gy absorbed dose prescribed to precancerous tissue (the dose-limiting tissue). In all cases DNA was extracted and bacterial diversity and taxonomic abundances were characterized by sequencing the 16S rRNA gene. During the cancerization process, we observed that Proteobacteria, Firmicutes and Actinobacteria decreased, while Bacteroidea and Fusobacteria increased (both previously reported in oral cancer patients). Oligo-Fucoidan treatment increased Proteobacteria 4 times ($p<0.01$) and reduced Bacteroidea 1.4 times ($p<0.05$). Besides, Oligo-Fucoidan tended to reduce Fusobacteria in cancerized pouches. As to BNCT, we observed that 2 h after BNCT there were no differences at phylum level vs cancerized animals pre BNCT. 24 h after BNCT a tendency to fusobacteria reduction was observed. 10 days after BNCT, in the peak of mucositis severity and incidence, fusobacteria increased. 10, 14, 28 days after BNCT, bacteroidea decreased and proteobacteria increased, tending to normal microbiota relative abundances. These preliminary results showed that DMBA cancerization process, Oligo-Fucoidan and BNCT changed phylum relative abundances of oral microbiota of the hamster cheek pouch. Ongoing studies are currently under evaluation related to the effect of BNCT+Oligo-Fucoidan on hamster oral microbiota. The significance of this study is that no reports were found in the literature related to the effect of BNCT on oral microbiota, an aspect that is conceivably of relevance in the outcome of treatment.
Acknowledgments: Hi-Q Marine Biotech (Taiwan).

Keywords: OSCC, oral microbiota, BNCT, hamster

Plenary 18

The feasibility study of BNCT for thoracic tumors: treatment planning aspect

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[Purpose] The accelerator-based boron neutron capture therapy (BNCT) for locally advanced or recurrent head and neck cancers is currently covered by insurance in Japan. In addition, using another accelerator-based BNCT system (CICS-1, manufactured by Cancer Intelligence Care Systems, Inc.), a phase II clinical trial for angiosarcoma is being conducted at the National Cancer Center Hospital, Tokyo, Japan (NCCH). In order to further expand the BNCT indications, we evaluated the tumor and organs at risk (OARs) doses of BNCT for breast, lung, and esophageal cancers in this study by treatment planning and examined the feasibility of BNCT in those cancers.
[Materials & Methods] Fourteen patients who received radiotherapy in NCCH were applied to this dosimetric study. The number of patients with breast, lung, and esophageal cancer were 6, 5, and 3, respectively. RBE-weighted equivalent dose distributions in each patient were calculated by using CT images via a Monte Carlo simulation code (PHITS, ver. 3.02). Although the treatment was usually assumed to be performed with single-fraction from a single beam direction, two-fraction treatment was also considered in 6 patients (breast: 1, lung: 4, esophageal: 1) to acquire the adequate dose distribution. It was noted that the different beam angles were assigned in each fraction. The equivalent dose of gross tumor volume (GTV) and OARs (liver, heart, lung, and oral mucosa) were evaluated with prescribing the maximum dose (Dmax) of 18 Gy-Eq to skin. Furthermore, considering the tolerance doses which the mean dose (Dmean) to the liver was 5.0 Gy-Eq[1)], the dose prescriptions were changed to meet the dose constraint in each OAR. MIM maestro (ver. 7.2.7, MIM software Inc.) was used to evaluate the equivalent dose distribution.
[Results & Discussion] In case of prescribing the Dmax of 18 Gy-Eq to the skin, the median of minimum dose (Dmin) to GTV was 48.2 Gy-Eq (range: 21.1-122.7). Furthermore, the median of the Dmean of heart, lungs, and liver was 5.5 (1.36-10.1), 8.6 (3.34-14.0), and 7.0 (3.5-14.3) Gy-Eq, respectively, and the median of Dmax of oral mucosa was 15.8 Gy-Eq (4.91-24.6). Some cases exceeded the tolerance dose of OARs. Thus, prescribing the Dmean of 5 Gy-Eq to the liver and, the median of Dmin of GTV was 34.6 Gy-Eq (20.9-64.1). When the dose prescription was appropriately performed considering the tolerance doses in each OAR by one- or the two-fraction treatment for each patient, the median of Dmin of GTV converted to equivalent dose in 2 Gy fraction (EQD2, α/β = 10 Gy) was 145.1 (39.1-289.0) Gy-Eq. In most patients (12/14, 85.7%), the EQD2(α/β = 10 Gy) exceeded 50 Gy-Eq of which the dose corresponded to the single fraction dose of 20 Gy[2)]. Alternatively, 6 treatment plans that have two-fraction were re-evaluated, assuming one-fraction treatment for each beam. Then, the median of Dmin of GTV was 17.6 (2.08-36.51) Gy-Eq. Hence, it would be possible to assure the dose of GTV for thoracic cancers considering the two-fraction treatments of BNCT and to satisfy dose constraints of OARs. However, in this study, the CT images in the supine position were used to make the treatment planning of the two-fraction treatment. So, it might be necessary to change the setup position.
[Conclusion] This study investigated the possibility of BNCT for thoracic cancer on the treatment planning. It was expected that by changing the appropriate dose prescription and number of treatment fractions according to the patient's condition, BNCT for the thoracic cancers could be performed safely while delivering the sufficient dose to the tumors.

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Keywords: Accelerator-based BNCT,Treatment planning,Monte Carlo simulation

Plenary 19

Optimized sulfamido-carborane-conjugated Gd complex as a theranostic probe for MRI-guided BNCT in mesothelioma therapy

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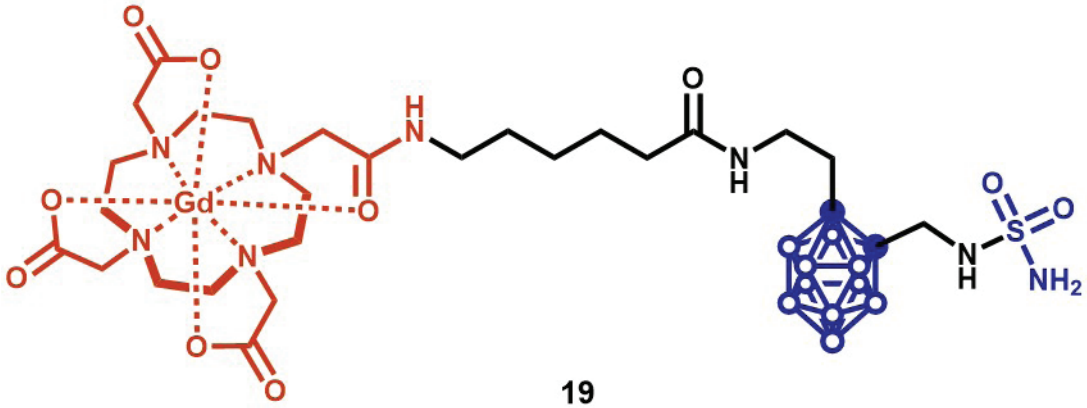

Figure captions: Figure 1. Structure of Gd-DOTA-CA-SF

This study proposes the characterization of a new multi-tasking agent, combining imaging and therapeutic properties, to enhance the efficacy of Boron Neutron Capture Therapy (BNCT) in cancer treatment. The agent Gd-DOTA-CA-SF (Figure 1) comprises a carborane unit (ten boron atoms for BNCT) linked to a sulfonamide group[1] on one side, designed to target and inhibit the enzyme carbonic anhydrase IX (CA IX)[2], which is overexpressed in various aggressive tumors, including mesothelioma and breast cancer. On the other side, the agent features a Gd(III)/1,4,7,10-tetraazacyclododecane monoamide (DOTA) complex as an MRI reporter for quantitative assessment of the B/Gd concentration. The use of these theranostics offers two primary advantages: firstly, dual Gd/B compounds exhibit a higher NCT efficacy when compared to systems comprising boron alone. This is attributable to the pronounced thermal neutron cross-sections of the two stable gadolinium isotopes (^{155}Gd and ^{157}Gd), providing a remarkable 65-fold improvement over ^{10}B in the case of ^{157}Gd. Furthermore, the incorporation of an MRI probe is crucial in ascertaining the precise concentration of the drug that has been internalized within the cancerous cell[3]. Moreover, administering dual Gd/B compounds enables the precise modulation of the neutron dose based on the exact amount of internalized ^{10}B, thereby avoiding undesired side effects induced by excessive irradiation. The longitudinal relaxivity ($1/T_1$) of Gd-DOTA-CA-SF measured at 0.5T and 25°C was 5.5 $mM^{-1}s^{-1}$, significantly exceeding the values of commercially available contrast agents (4.3-4.7 $mM^{-1}s^{-1}$). This enhanced efficiency can be attributed to the higher molecular weight of Gd-DOTA-CA-SF, which contributes to a reduced tumbling time of the complex. Interestingly, this is the first instance of a sulfonamide-carborane inhibitor moiety being conjugated to a hydrophilic Gd-complex. A notable advantage of this conjugation is the improved solubility of the complex, eliminating the need for solubilizing agents such as β-cyclodextrins or nanosized carriers. In vitro studies, evaluating the inhibition of esterase activity by the CAII and CAIX enzymes, confirmed the preservation of the inhibitory effect of the sulfonamide moiety even after its binding to the Gd-complex. Cell uptake studies conducted on mesothelioma cells revealed that the amount of boron internalized into tumor cells is sufficient for effective BNCT. Neutron irradiation will be performed on mesothelioma cells and compared with the side effect observed on healthy cells. In conclusion, an accurate treatment planning is crucial for mesothelioma, a malignant neoplasm of mesothelial cells caused by asbestos exposure and currently without a definitive cure. The average survival after diagnosis is often limited to nine to twelve months. A multi-faced therapeutic approach is therefore necessary to manage mesothelioma and reduce the risk of recurrence.

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Plenary 20

EXPLOITING BORON NEUTRON CAPTURE THERAPY (BNCT) AGAINST AMYLOID AGGREGATES

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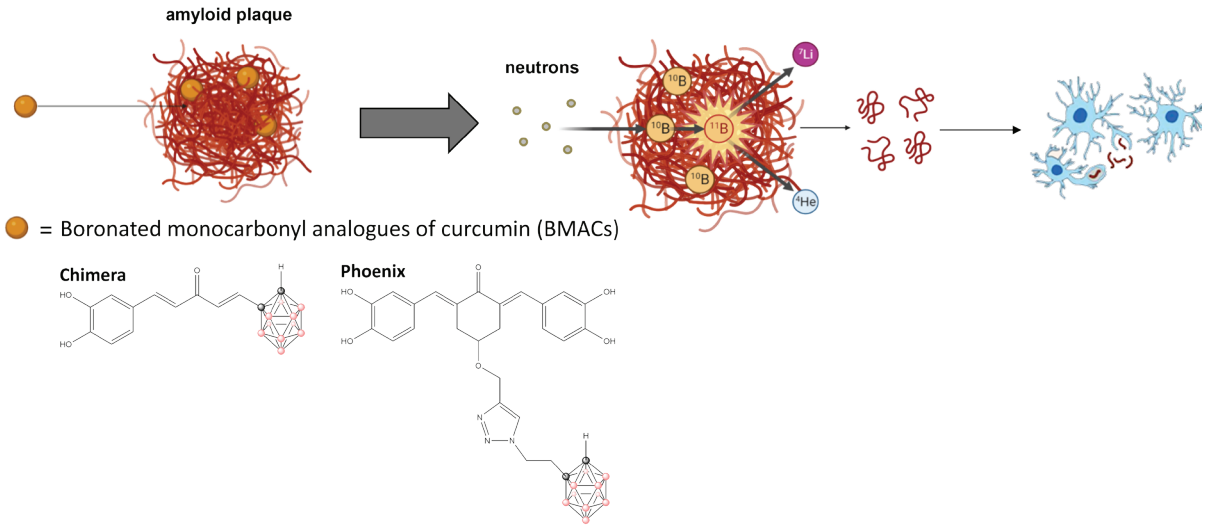

Figure captions: BNCT approach scheme on Amyloid-beta aggregates using BMACs.

Alzheimer's disease (AD) is a progressive neurological illness characterized by language difficulty, disorientation, irreversible memory loss, and cognitive decline. Despite the high impact of AD on patients and care, its etiological mechanism remains unclear. The approved drugs can only alleviate its symptoms and not terminate or reverse the progression of the disease. According to the amyloid-β (Aβ) hypothesis, the primary cause of AD pathogenesis is Aβ accumulation in the human brain. While Aβ species has multiple isoforms, the most common are Aβ-40 and Aβ-42, with Aβ-42 being the most prone to aggregation, forming oligomers, protofibrils, and fibrils. The Aβ fibrils can accumulate, finally forming larger Aβ deposits called Aβ plaques, one of AD's main hallmarks. Among these different kinds of Aβ aggregates, oligomers have been shown to have a strong neurotoxic effect, moreover, fibrils can fragment and release them, serving as an oligomers reservoir [1]. The aim of this study is the preparation, characterization, and validation of a new class of carborane-containing compounds able to selectively bind to Aβ oligomers and fibrils to be used for AD treatment and prevention. The disaggregation of Aβ fibrils will be obtained by exploiting the synergy between an external beam of low-energy neutrons and these specifically engineered agents capable of selectively binding to the Aβ aggregates. In this regard, curcumin's affinity for Aβ fibrils and its therapeutic effects for AD have made it a study priority. Recently, there have been some questions concerning Curcumin efficacy due to its instability caused by the high reactivity of the β-diketone moiety. For these reasons, many efforts have been devoted to the synthesis of Curcumin analogues that can improve molecular stability such as monocarboranyl 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 (BMACs) that contain an ortho-carborane [2]. Aβ-42 peptide has been incubated in physiological-mimicking conditions for several days, to have Aβ aggregates in protofibrillar and fibrillar state [1,3]. Following this, Aβ aggregates were characterized using FESEM microscopy and a spectrofluorometer with thioflavin T as a reference dye. The affinity of the compounds for the Aβ aggregates has been evaluated by competition assay using a spectrofluorometer and thioflavin T as a reporter dye. Inhibition constant values, derived by the Cheng-Prusoff equation [4], showed the BMACs' affinity for the aggregates. Neutron irradiation has been performed on Aβ aggregates samples treated with BMACs and analyzed by a semi-quantitative method using FESEM microscopy. A significant disaggregation effect was observed only in the samples treated with both neutrons and BMAC. The irradiated samples have been analyzed also by 1H-NMR spectroscopy to identify the possible chemical changes in the protein structure. These preliminary studies have shown the disaggregation effect of BNCT on Aβ aggregates. Preliminary results, showing structural damage of beta-amyloid (Aβ) aggregates induced by ionizing radiations generated by neutron capture, will be also described. The next step will be to optimize the irradiation therapy to get closer to a clinical approach.

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Keywords: Curcumin, MAC (Monocarbonyl analogues), BMAC

Plenary 21

Treatment Planning System for BNCT – presentation of the current achievements of the TPS Task Group of the BNCT Polish Consortium

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The prediction of spatial, 3-dimmentional (in-tissue) dose distribution is an essential step in the preparation of conventional treatment in radiotherapy of oncological diseases. The computer programs usually known as Treatment Planning Systems (TPS's) are used for this purpose. In Boron Neutron Capture Therapy (BNCT) such a TPS is also required. The TPS must be able to simulate the penetration of a neutron stream into the patient's body and determine the dose resulting from their interaction with matter (for both both: the tissue containing the B-10 isotope and normal tissue). In order to determine the absorbed dose (and biological dose), the TPS must use input data that qualitatively describe the neutron stream (the beam fluence and its spectrum), CT or MRI anatomical reconstructions of the patient body (including information ot boron distribution and tissue density) and physical models of interactions occurring as a result of collisions occurring in tissues. On this basis, the TPS determines the impact of the dose deliverred by alpha particles and other ions, as well as gamma radiation produced in the process. The TPS contains basic tools for the spatial analysis of dose distribution, similar to TPS systems used in conventional radiotherapy using the so-called external beams to enable comparison of BNCT with traditional treatment. The System implements the achievements of the working groups of the Polish Consortium for BNCT: the group responsible for beam dosimetry, the group responsible for patient scanning, the group responsible for modeling the interaction of neutrons with tissue and the clinical group, which will be presented in the context of TPS. As a result of TPS work, a set of radiation exposure data is generated (e.g. irradiation time and field of irradiation parameters such as optimal direction and dimmentions) and the necessary data to perform the dedicated "in vivo" verification of the treatment.

Keywords: treatment planning, dose distribution, clinicalspects

Plenary 22

Gold nanoparticles as radiosensitizers – the influence on breast cancer cells in Boron-Neutron Capture Therapy

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Introduction: Boron-Neutron Capture Therapy (BNCT) is one of the hadrontherapy treatment methods. It is based on the ability of non-radioactive boron-10 isotope to capture thermal neutrons. The effectiveness of BNCT is dependent on cellular uptake of boron carrier which differs among cells. In the experiment, luminal subtype (MCF-7) and triple-negative subtype (MDA-MB-231, MDA-MB-468) of breast cancer cell lines were used. Moreover, cancer cells were sensitized by two different sizes of gold nanoparticles: 50 nm and 100 nm. As boron carrier, BPA (p-borophenylalanine) was used. Gold nanoparticles were used as a sensitizers due to their characteristic properties such as low toxicity and biocompatibility. The main aim of the research was to analyze the influence of gold nanoparticles on the sensitivity of breast cancer cells in the case of treatment with BNCT.

Methods: Breast cancer cells were irradiated after 4 h and 24 h incubation time with GNPs. BPA was added 4 h before irradiation to each sample containing medium with gold nanoparticles. Cells were exposed to neutron radiation in MARIA research reactor (located in National Centre for Nuclear Research in Świerk, Poland) with absorbed dose corresponding to 2-2,5 Gy. Cell cycle distribution and apoptosis assays were performed 24 h post irradiation with the usage of flow cytometry. Clonogenic assay was carried out 24 h after irradiation and counting of colonies was conducted in 3-week time. MTT cytotoxicity assay was performed 24 h after irradiation. Micronuclei assay was conducted in 30 h, 36 h and 42 h after irradiation. Gamma-H2AX assay was performed 24 h post irradiation by flow cytometry method.

Results: Results show there was none significant difference between trials of MDA-MB-231 in apoptosis level, whereas in MCF-7 cells, there were differences between trials in the level of late apoptotic and necrotic cells. In clonogenic assay, both types of cells shown significant decrease in the survivability rate after irradiation with addition of GNPs. Cell cycle distribution assay has shown that MDA-MB-231 cells are blocked in G2 phase of cell cycle after irradiation, whereas in MCF-7 were samples where the cell cycle is not blocked completely. In the case of MTT assay, the results would be presented at the conference. Micronuclei assay has shown that the highest frequency of micronuclei was observed in trials 36 hours after irradiation. 42 hours after irradiation, micronuclei frequency has decreased almost to the level which was after 32 hours post irradiation. In the case of gamma-H2AX assay results, there was noticeable difference in the fluorescence level of gamma-H2AX foci especially in the case of triple-negative subtype breast cancer cell. In the case of size of gold nanoparticles, better effectiveness of the treatment in each assay were observed in the trials with addition of 100 nm GNPs.

Conclusion: Obtained results demonstrate that gold nanoparticles are improving the effectiveness of BNCT especially in the case of triple-negative subtype of breast cancer cells. It is noticeable that MDA-MB-231 cells were better reacting for BNCT treatment with gold nanoparticles than MCF-7. However, the exact cause of such results currently is unknown and there is a need for further research in that topic. In the future, it is planned to assess the normal cells toxicity of the treatment and perform the experiment on the tissues from oncological patients.

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Keywords: GNPs, TNBC, , TNBC, sensitization

ORAL PRESENTATIONS

Clinical Trials & Routine Practices

Preliminary Outcomes of Boron Neutron Capture Therapy for Head and Neck Cancers as a Treatment Covered by Public Health Insurance System in Japan: Real-world Experiences Over a Two-year Period

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Purpose: Boron neutron capture therapy (BNCT) is a treatment in which compounds containing boron (^{10}B) are incorporated into tumors followed by subsequent irradiation with thermal neutrons (1). BNCT for head and neck cancers began in Japan in 2001 ahead of the rest of the world (2), and thereafter, has been used in Finland and Taiwan. Previous trials have shown satisfactory results (3); however, at the time, neutron irradiation required a nuclear reactor, therefore BNCT could not be used as a general treatment and remained merely a special-case experimental procedure. To address this clinical difficulty, an accelerator (cyclotron) based BNCT system was developed by the Kyoto University Group in collaboration with Sumitomo Heavy Industry, Ltd. (Tokyo, Japan) in 2008. Since June 2020, BNCT has been a healthcare service covered by health insurance in Japan to treat locally advanced or recurrent unresectable head and neck cancers (4). Therefore, we aimed to assess the clinical outcomes of BNCT as a health insurance treatment and explore its role among the standard treatment modalities for head and neck cancers.

Materials and Methods: We retrospectively analyzed data from patients who were treated using BNCT at Kansai BNCT Medical Center, Osaka Medical and Pharmaceutical University, between June 2020 and May 2022. We assessed objective response rates based on the Response Evaluation Criteria in Solid Tumors version 1.1, and adverse events based on the Common Terminology Criteria for Adverse Events, version 5.0. Additionally, we conducted a survival analysis and explored the factors that contributed to the treatment results.

Results: Sixty-nine patients (72 treatments) were included in the study, with a median observation period of 15 months. The objective response rate was 80.5%, and the 1-year locoregional control, progression-free survival, and overall survival rates were 57.1% (95% confidence interval [CI]: 43.9–68.3%), 42.2% (95% CI: 30.1–53.8%), and 75.4% (95% CI: 62.5–84.5%), respectively. Locoregional control was significantly longer in patients with earlier TNM staging and no history of chemotherapy.

Conclusions: BNCT may be an effective treatment option for locally advanced or recurrent unresectable head and neck cancers with no other definitive therapies. However, if definitive surgery or radiation therapy are not feasible, BNCT should be considered at early disease stages.

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Keywords: ABBNCT, H&NCancer, health insurance treatment

Clinical Use of Sodium Borocaptate as a Boron Delivery Agent for Neutron Capture Therapy of Brain Tumors: Pioneering Studies that Provided a Path to the Future

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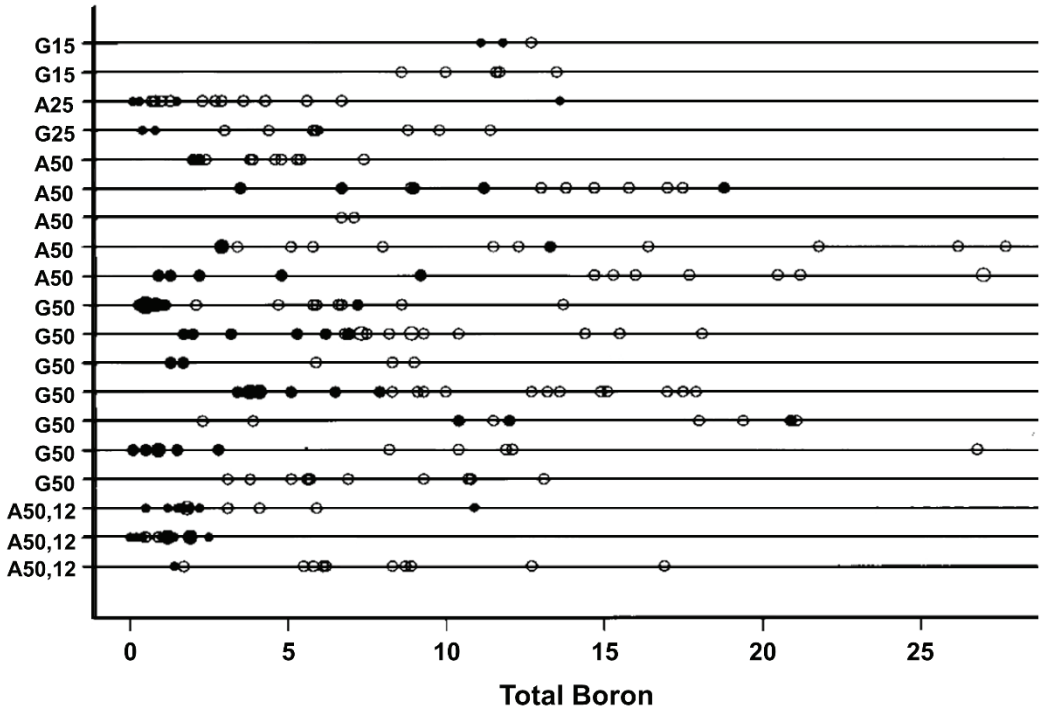
Study Goal	Samples to collect and analyze
Pharmacokinetic studies with at least 3 dose levels of the boron delivery agent	Sampling of blood and urine for 120 hours following administration for boron determination. Blood samples should be collected in heparinized tubes at the start of the infusion and 15 and 30 minutes, and 1, 2, 4, 7, 13, 24, 48, 72, 96 and 120 hours following the infusion to calculate the pharmacokinetic profile of the agent
Define excretion profile of the boron delivery agent	Urine should be collected for each 24-hour interval for 5 days.
Boron in tumor	Multiple samples of the resected tumor, as well as infiltrating and necrotic tumor and a mixture thereof
Extra-tumoral boron determinations	On samples of skin, bone and muscle, which may be taken as part of the operative procedure

*As reported by Goodman et. al. the patient should be informed that all the following will not have any impact on their treatment.



Dot plot of individual patients' total boron values (µg/g) for astrocytomas (A) and glioblastomas (G) (solid tumor) and normal brain. Patients received dose of 15, 25, or 50 mg B/kg b.w., and tissues were sampled 3-7 hours following termination of the infusion except for an additional group of 3 patients with astrocytomas, from whom tissue samples were taken after 12 hours (A 50,12). Normal brain values are indicated by •, and tumor values by ○. Larger circles (○ or ●) indicate 2 identical values, and the largest circles (○, ●) indicates 3 identical boron values. The mean total boron concentrations (µg/g) for normal brain and solid tumor are plotted on the 2 bottom lines.

Figure captions:
Table 1: Stepwise plan for the clinical evaluation of new boron delivery agents.*
Figure 1. Dot plot of individual patients' total boron values
Sodium borocaptate, BSH, was the first drug used clinically for BNCT of patients with recurrent brain tumors. The basic studies leading to this were carried out in Soloway's laboratory in the Department of Neurosurgery at MGH. These were initiated

by Hatanaka, a visiting Japanese neurosurgeon, who evaluated a group of boron hydride anions, among which was $Na_2B_{12}H_{11}SH$ or "BSH" [1]. The major focus of their research was to identify boron compounds that potentially could be used as a boron delivery agents for BNCT. In vivo studies, carried out in C3H mice bearing implants of an ependymoblastoma, revealed that this compound selectively attained high tumor concentrations and low blood boron concentrations [1]. Upon his return to Japan Hatanaka carried out a series of studies that established the safety and potential efficacy of BSH to treat patients with primary brain tumors. He started treating patients with gliomas in 1968 using BSH. Between 1968 and 1985 a total of 77 patients with brain tumors of varying histopathologic types, and among these purportedly were high grade III – IV gliomas were treated [2]. Initially BSH was administered via the carotid or vertebral arteries and subsequently i.v. at a later point in time. The five and 10 year survival rates of the first group of 77 patients were 58% and 29%, respectively [2]. As it turned out these survival data were too good to be true. Most likely, the majority of these patients had lower rather than higher grade III-IV gliomas. Nevertheless, his results were impressive enough to stimulate a renewed interest in BNCT. Almost 10 years after Hatanaka's original report [2], Hatanaka and Nakagawa provided an update [3]. Between 1968 and 1997 a total of 173 patients received BNCT following "debulking" surgery. A more realistic picture of the histopathologic diagnoses revealed that of those patients who lived more than 3 years only 10 of 81 had glioblastomas (GBMs) [4]. However, the 3 year survival rates were at least as good as patients who had received conventional therapy.

The only other BSH clinical study was carried out by Wittig, et. al. in an EORTC study – 11961 [5]. BNCT was given in 4 fractions on 4 consecutive days. However, their results were no better than those reported for patients treated with conventional therapy. The disappointing clinical results obtained could have been predicted based on a number of pharmacokinetic and biodistribution studies, the most detailed of which was the one carried out at OSU in collaboration with the Beijing Neurosurgical Institute [6]. Of the 25 patients, 19 had GBMs or anaplastic astrocytomas (AAs). Most importantly, because this was a biodistribution and pharmacokinetic study, it had no effect of the type of adjuvant therapy after surgery. Patients were stratified into 3 dosage groups receiving BSH i.v.. Blood boron concentrations were highest at the end of infusion and then decreased tri-exponentially. Multiple samples of each tumor revealed significant variability in their boron concentrations (Fig1). When averaged over all of the tumor samples of AAs and GBMs at 3 to 7 h after infusion the mean tumor boron concentration values were 11.9 µg/g and normal brain values were 5.5 and 4.6 µg/g for AAs and GBMs, respectively. Taking all of the tissue and blood boron values together, the best values were seen at a dose of BSH of 25 mg/kg b.w. at 3 to 7 h following administration of BSH. These were lower than those required for a tumoricidal effect. However, most importantly Goodman et. al's study provided a template on how new boron delivery agents should be evaluated clinically [6] and opened up a path to the future.

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Clinical Use of Boronophenylalanine as Boron Delivery Agents for Neutron Capture Therapy

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The pioneering studies of Yukata Mishima et. al. led to the introduction of 4-boronophenylalanine ("BPA") first for the treatment of cutaneous melanomas [1] and subsequently for other types of cancers, most important of which were high grade gliomas and recurrent tumors of the head and neck region. Coderre et. al. [2] were the first to demonstrate that BPA was effective in treating rats bearing intracerebral implants of the highly immunogenic 9L gliosarcoma [3]. These studies laid the groundwork for the most comprehensive clinical pharmacokinetic and tissue biodistribution studies of BPA in patients with glioblastomas (GBMs), which was carried out by Elowitz et. al. [4]. Varying doses (130 -250 mg/kg b.w.) of a fructose complex of BPA were administered i.v. 2-3 hours prior to the start of craniotomies of 16 patients with GBMs. Multiple samples of tumor, brain and scalp were taken at surgery for boron determinations. Blood clearance of boron was biphasic with a first phase (re-distribution) having a half time ($T_{½}$) of ~1.2 hrs lasting 30 to 40 minutes. The second phase (elimination) had a $T_{½}$ of ~8.2 hrs. There was a high degree of variability in the tumor boron concentrations in multiple samples taken from the same patient, as well as patient to patient variability[4]. Similarly, tumor:blood boron concentration ratios were highly variable and appeared to be related to the cellularity of the tumor samples [5]. Normal brain boron concentrations were either less than or equal to those seen in the blood. Tumor:blood ratios were highly variable from patient to patient and ranged from 0.3 to 3.5. Nevertheless, the data obtained were encouraging enough to initiate a Phase I/II clinical trial in the Medical Department of Brookhaven National Laboratory, using the Brookhaven Medical Research Reactor (BMRR). However, the results of this trial were not particularly encouraging. The median time to progression and median survival time of 37 patients treated at the BMRR were 31.6 weeks and 13.0 months, respectively. Local control and survival times were similar to those of historical controls at the time the study was carried out between 1994 and 1999 [6]. These clinical results probably could have been predicted based on the biodistribution and tumor uptake data reported by Elowitz et. al [4] and subsequently by Coderre et. al. relating to tumor cellularity[5]. Nevertheless, they laid the groundwork for a number of studies carried out in Japan, Finland, and Sweden and the United States. Sadly, there is a paucity of other data similar to that reported on the tumor vs. normal brain uptake of BSH [7] and that reported by Elowitz et. al. [4] on the tumor vs. normal brain uptake of BPA in patients with brain tumors. The evaluation of BPA, as described by Elowitz et. al. [4]and Coderre et. al. [5], and BSH by Goodman et. al. [7] provides a plan for the future clinical evaluation of the most promising of the hundreds of agents that have been described in the chemical and biological literature The logistics of carrying out such clinical studies have been described by Elowitz et. al. [4] and in even more detail by Goodman et. al.[7]. Unfortunately, however, both Goodman et. al and Elowitz et. al. studies were published in the non-Open Access journal, Neurosurgery, which limited their accessibility, even today. We hope that this short review will make available to a broad audience of readers interested in BNCT of what needs to be done to clinically evaluate the most promising of the 100's of boron delivery agents that, as yet, are still in an early stage of pre-clinical evaluation.

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Results of investigator-initiated trials on boron neutron capture therapy for brain malignant tumors and recurrent head and neck malignant tumors Junqiang Hong[1]
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Introduction NBB-001-BNCT-H-HN/MG-001

Name		**Safety and Efficacy of Boron Neutron Capture Therapy for Advanced Refractory Malignant Tumors : A Single-center, Single-arm Trial**
PI		**Pan Jianji & Huang Cheng**
Sample size		**n = 14**
Indications		**Relapsed and refractory head and neck MTs & Primary brain MTs**
Period		36 Months
Type		Investigator-initiated Clinical Trial (IIT)
Objectives	**Major objective**	**Evaluating the safety of BNCT**
	Secondary objective	(1) Evaluating the ORR of patients 90 days after BNCT (2) Evaluating the stability, failure occurrence and overall performance of the AB-BNCT equipments
	Exploratory objective	(1) Preliminary exploration of the pharmacokinetic characteristics of NBB-001 (2) The correlation between tumor biomarkers and prognosis before and after BNCT

Figure captions: Introduction NBB-001-BNCT-H-HN/MG-001

Results of investigator-initiated trials on boron neutron capture therapy for brain malignant tumors and recurrent head and neck malignant tumors

Abstract:
Background: Boron Neutron Capture Therapy (BNCT), a novel approach offering targeted radiation therapy, has shown promise in minimizing damage to healthy surrounding tissues[1]. In China, the clinical implementation of BNCT has made certain progress[2]. However, there is a lack of human experimental results on BNCT's effectiveness against brain malignant tumors (MTs) and recurrent head and neck MTs.

Objective: This study aims to assess the safety and efficacy of BNCT in treating brain MTs and recurrent head and neck MTs.

Methods: The study enrolled 14 patients from October 9, 2022, to April 11, 2023, at Xiamen Humanity Hospital, administering 18 BNCT treatments. This included 7 cases each of relapsed/refractory head and neck MTs and primary brain MTs. Patients were divided into two dosage groups: 500mg/kg (11 patients) and 750mg/kg (3 patients).

Results: Over a median follow-up of 7 months, the median dose received by 80% of the target volume was 16.80GyE (8.93~23.79GyE, GyE:Equivlant dose). Side effects mostly remained below grade 3, including gastrointestinal reactions (78.6%), intracranial hypertension (42.9%), hyperamylasemia (78.6%), hyperprolactinemia (50%) and alopecia (71.4%). There were 8 adverse reactions over grade 3 in 5 patients, and all recovered after observation or treatment. The Objective Response Rate (ORR) was 64%, and the Disease Control Rate (DCR) was 71%, with complete responses in 2 patients (28.57%) with brain MTs and 1 patient (14.29%) with recurrent head and neck MTs.

Conclusion: BNCT demonstrates a favorable safety profile and potential efficacy in extending survival among patients with brain MTs and recurrent head and neck MTs. This suggests BNCT as a viable treatment option, especially for patients lacking standard treatment options.

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Keywords: BNCT, brain malignant tumors, head and neck malignant tumors, safety, efficacy.

Long-Term Results of Accelerator-Based Boron Neutron Capture Therapy (AB-BNCT) for Recurrent Malignant Gliomas: A Phase II Study Utilizing Cyclotron-Based Neutron Source (BNCT30) and Boronophenylalanine (SPM-011)

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Purpose: The Regulatory approval of accelerator-based neutron sources has facilitated the incorporation of Boron Neutron Capture Therapy (BNCT) for head and neck cancer into clinical practice. This study aims to emphasize the effectiveness of AB-BNCT, particularly in the context of highly invasive malignant gliomas (MG), by presenting the long-term results of a phase II trial utilizing a cyclotron-based neutron source (BNCT30) and boronophenylalanine (SPM-011) in patients with recurrent MG.

Methods: The JG002 phase II clinical trial enrolled 27 patients with recurrent malignant glioma (24 with glioblastoma (GB)), employing SPM-011 and BNCT30. Eligible patients had undergone radiation re-irradiation for MG not previously treated with bevacizumab, experiencing relapse after standard care (radiotherapy and chemotherapy with temozolomide). The primary endpoint was one-year survival from BNCT treatment, with secondary endpoints being median overall survival (mOS) and median progression-free survival (mPFS).

Results: In JG002, patients with relapsed GB exhibited a 1-year survival rate of 79.2% (95% CI: 57.0-90.8) and mOS of 18.7 months. Long-term observations revealed mOS of 19.2 months (95% CI: 13.1-24.8), with 2 and 3-year survival rates of 33.3% and 20.8%, respectively. Cerebral edema was the primary adverse event, prompting bevacizumab treatment in 21 of 27 patients following disease progression (PD) on imaging.

Discussion: Although the secondary endpoints of PFS and response rate, based on RANO criteria, were notably poor (PFS: 0.9month, 95% CI: 0.8-1.0 and response rate: 0%), there was a significant improvement in life expectancy. This suggests the challenge of evaluating this therapy, particularly for central nerve system (CNS) tumors, using existing imaging methods. This issue has been frequently raised and has also become a concern in angiogenesis-inhibiting therapy and recent immunotherapy for CNS tumors. It has led to the proposal of an optimized evaluation method instead of the previously commonly used image evaluation criteria for other solid cancers. The substantial difference between OS and PFS in this study indicates an antitumor effect that is challenging to evaluate using the standard image evaluation criteria in clinical trials, such as RESICT and RANO, to assess tumor reduction / enlargement in MG. Due to these evaluation challenges in radiographical endpoints, this BNCT trial reported a much shorter PFS than OS. However, in reality, the patient's Karnofsky Performance Status (KPS) did not decline after the decision of progression based on imaging studies, as demonstrated in the present study. Nevertheless, as shown in this study, adequate attention and assessment should be given to prevent the occurrence or worsening of peri-tumoral edema.

Conclusion: AB-BNCT demonstrated acceptable safety and conferred a survival benefit in relapsed MG, predominantly GB. Post-BNCT treatment, tumor contrast enhancement in the irradiated field, coupled with brain edema, was noted. The study indicates sustained survival benefits from BNCT in patients with recurrent malignant gliomas over the long term. Limitations and future prospects: The interpretation of the clinical trial results warrants careful consideration. The observation of an early switch to bevacizumab in the majority of patients experiencing pseudo-progression in imaging suggests the possibility that the addition of bevacizumab shortly after BNCT may confer an adjuvant effect. Therefore, the observed effect of BNCT combined with bevacizumab requires further investigation, including the examination of a separate cohort that did not receive bevacizumab. Assessing the efficacy of pure BNCT re-irradiation is challenging, particularly if true progression is delayed. Moving forward, ongoing discussion regarding future prospects is essential.

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Early Clinical Experience of Boron Neutron Capture Therapy: Compassionate Use Cases in South Korea

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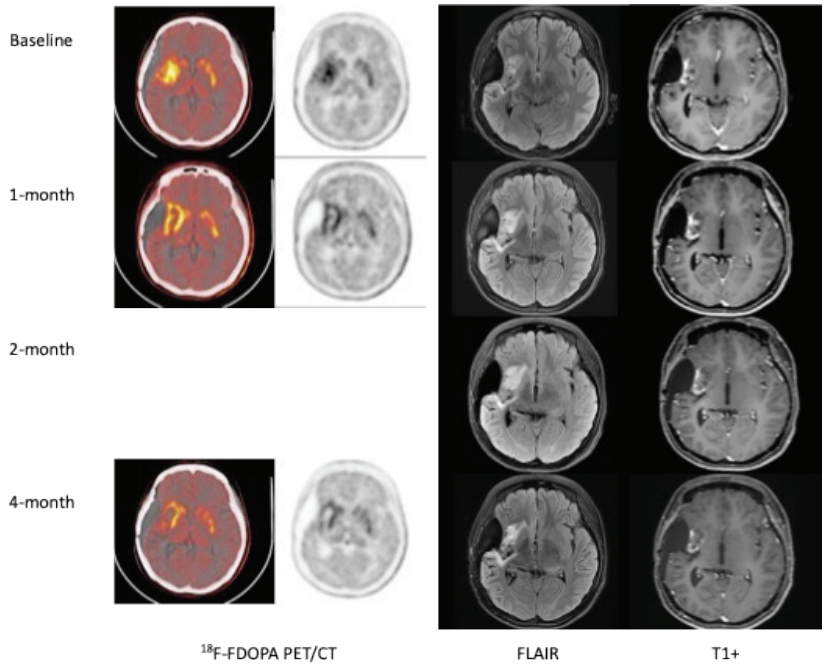

Figure captions: Case example of pediatric patient with diffuse pediatric high grade glioma, H3-wild type, IDH wild type, WHO grade 4. Patient with history of CCRT in '22.09-11 and BNCT was provided after recurrence.

Boron Neutron Capture Therapy (BNCT) represents a revolutionary approach in the field of radiotherapy, leveraging the unique properties of boron-10 isotopes to selectively target and obliterate malignant cells while preserving the integrity of the surrounding healthy tissue. As a binary treatment modality, BNCT requires both the presence of a boron-containing compound preferentially absorbed by cancer cells and subsequent irradiation by low-energy thermal neutrons. The interaction between the neutrons and the boron-10 creates high-energy alpha particles and lithium nuclei, which possess a limited range, thus confining their destructive impact to the cellular level.
This advanced treatment approach is currently the subject of intensive research and clinical trials, particularly focusing on its efficacy in managing recurrent high-grade gliomas – a formidable challenge in oncologic care due to their aggressive nature and poor prognosis. Additionally, BNCT is in the recruitment phase of a Phase I trial aimed at assessing its therapeutic potential for patients with recurrent head and neck cancers. These malignancies, often characterized by their recurrence and resistance to conventional therapies, present a critical need for innovative treatment options.
Simultaneously, we are committed to extending the potential benefits of BNCT beyond the confines of clinical trials through an expanded access program, often referred to as compassionate use of investigational products. This initiative is especially targeted at individuals suffering from recurrent brain tumors who have exhausted standard treatment options and are seeking alternative therapies. As we continue to collect and analyze data, we are expanding this compassionate use to include cases of recurrent head and neck cancers, thereby offering hope to a broader spectrum of patients.
In this presentation, we will share a series of case studies from the compassionate BNCT treatment program. These real-world examples will provide valuable insights into both the promising benefits and the inherent limitations of this innovative therapy. By examining the treatment outcomes, patient responses, and unique challenges encountered, we aim to foster a comprehensive understanding of BNCT.
Moreover, the knowledge gained from these cases is instrumental in the ongoing refinement of BNCT protocols and strategies. Our goal is to optimize treatment outcomes, minimize adverse effects, and ultimately expand the applicability of BNCT to a broader range of patients in need. As we continue to advance our understanding and improve our techniques, BNCT stands on the cusp of transforming the landscape of cancer therapy, offering new hope to those battling the most challenging forms of this disease.

Keywords: Expanded access, case report

Interim results of accelerator-based boron neutron capture therapy, randomized controlled trial for recurrent and refractory high-grade meningiomas

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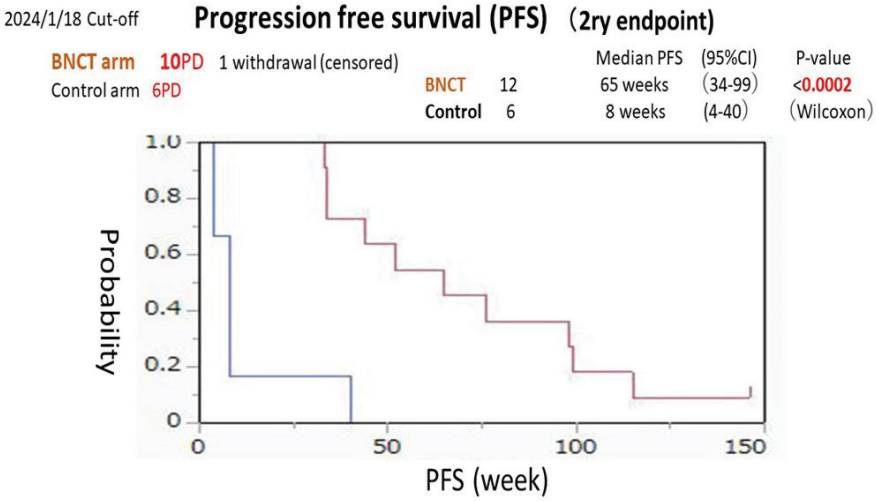

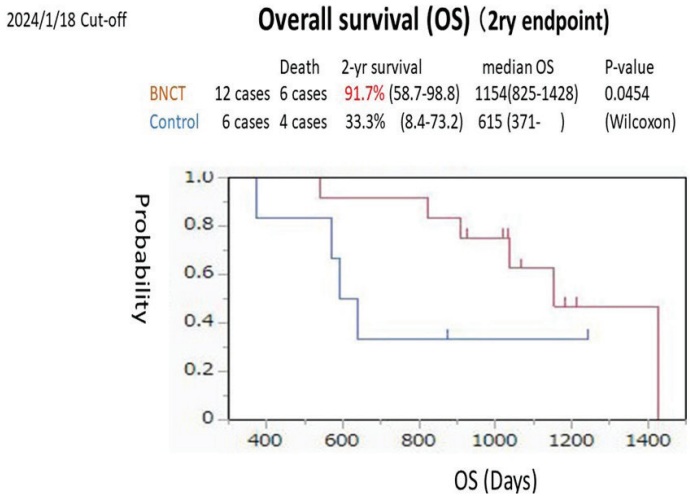

Figure captions:
Figure 1: Progression free survival of both arms judged by investigators (secondary endpoints)
Figure 2: Overall survival of both arms. OS of BNCT arm is one of the secondary endpoints.

Introduction: High-grade meningiomas (HGMs) recurred after X-ray treatment showed 5.2 months as median progression free survival (mPFS) and only 24.6 months as median overall survival (mOS) from the literatures (1). Also, in the literature, the authority stated progression free survival rate at 6 months (PFS-6) > 35% is the recommendation for further clinical trials. Recently, we published much more excellent OS and PFS using reactor-based boron neutron capture therapy (BNCT) for refractory and recurrent HGMs (2). We showed excellent mOS and mPFS using 44 recurrent HGM in this report. PFS-6 was 80.6% of the cases. Based on these data, we started "A phase II investigator-lead RCT using accelerator-based BNCT system for refractory recurrent high-grade meningioma", with the aid of Japanese governmental financial support (AMED), with the negotiation and agreement of Japanese FDA (PMDA).

Materials and Methods: We prepared 2 study arms, BNCT test treatment arm (12 subjects) and control best supportive care arm (6 subjects) in randomized controlled trial (RCT) fashion. PFS judged by the third-party committee was set-up as primary endpoint and PFS judged by investigators themselves and OS of BNCT arm were set-up as secondary endpoints. To diminish ethical problems of this RCT, rescue BNCT is permitted for control group patients, if they showed progress disease (PD) during the observation period. Macdonald criteria was adopted for assessment. The first patient-in was August 2019 and the last patient-in was August 2021.
Interim results of this trial: Three and two grade 3 subjects were included in BNCT and control arm, respectively. Others were grade 2 subjects. As of January 18, 2024, 10 out of 12 cases in BNCT arm and all 6 cases in control arm were judged

as PD by investigators. mPFS judged by investigators showed 65 weeks and 8 weeks for BNCT and control arm, respectively (P=0.0002, Wilcoxon). Up to the same cut-off day, 6 out of 12 in BNCT and 4 out of 6 cases in the control arm were dead. OS-2 year rates of BNCT and control arms are 91.7% and 33.3%, respectively (p=0.045, Wilcoxon). Five out of 6 cases in control arm received rescue BNCT after PD assessments.

Conclusion: Primary endpoint, mPFS judged by third party committee is still being closed and unknown, so far, until the end of the trial (Autumn of this year). With regard to secondary endpoints, there are marked differences in both arms in mPFS judged by investigators. Recently, the results of RCT of "Trabectedine" organized by EORTC was reported.(3) Unfortunately there was no effect of Trabectedine with comparison of control arm not only in PFS but in OS. In our current RCT results BNCT arm is extremely excellent in comparison with EORTC RCT of "Trabectedine" (3) both in OS and PFS, amazingly.

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Keywords: accelerator-based BNCT, high-grade meninigioma, RCT

BNCT Phase I Clinical Trial for newly diagnosed Glioblastoma

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The University of Tsukuba has opened enrollment for a BNCT Phase I investigator-initiated clinical trial for first-diagnosed glioblastoma on a new development accelerator starting in December 2023. This protocol is available on the web by regulation (1). Patients must have a histologic diagnosis of IDH-wild type glioblastoma according to the WHO 2016 classification, and must still have postoperative imaging lesions to be eligible for enrollment. Treatment is BNCT (boron drug SPM-011, neutron source iBNCT-001) with external beam radiation and temozolomide after 7 days of BNCT treatment. Dose-limiting toxicities are a primary endpoint. Boron Drug dosing regimen is similar to that approved for head and neck cancer. Neutron dose regulation is defined by D2cc of normal brain on a newly developed treatment planning system. As the first step for medical device approval, a first in human phase I study will be set up to determine the recommended dose. A phase II study will then be conducted at the determined dose. This approach is similar to the process used when an accelerator-based neutron source was approved for head and neck cancer in Japan. The boron concentration 10 minutes before irradiation is measured from whole blood by ICP method, and the irradiation time is corrected by the result.
The chemo-radiotherapy to be administered in combination with BNCT is as follows 7days after BNCT, 40Gy (5fraction/week, 2Gy/fraction) external X-ray radiotherapy will be initiated; Temozolomide will be used during the X-ray treatment period at the usual dose, followed by maintenance therapy. Three doses will be titrated using a 3+3 algorithm, with the rate of appearance of dose-limiting toxicities as the primary endpoint. The evaluation period will be up to 24 months after BNCT. Thereafter, survival will be monitored until the end of observation of the last case. The pretreatment screening period will be 1 week, and the safety evaluation period will be 90 days after BNCT. Since iBNCT is a first-in-human device, the acute safety evaluation period: 35 days after BNCT will be used for confirmation. The efficacy evaluation period was set at a maximum of 24 months after BNCT was performed. If the patient is found to be PD by RANO criteria, the safety or efficacy evaluation period will be terminated, and the patient will be moved to the follow-up period to continue survival observation only. The plan is to enroll 12 to 18 patients through a 3-step dose escalation process to determine the recommended dose.
The concept of adding X-irradiation after BNCT is one that our university hospital has experience in treating several cases with nuclear reactors and is treated as part of Protocol -2 in Yamamoto et al.'s 2009 report on clinical researches and as Protocols III and IV in Nakai's report. (2)(3). A similar clinical research protocol has already been registered as a phase II study from Osaka Medical and Pharmaceutical University (OSAKA-TRIBRAIN0902, NCT00974987). According to the website (4), it was initiated in 2009 and patient enrollment has been completed at 2016, Only an interim evaluation was reported (3) and no final results were reported. Kawabata et al. (5) stated that Patients treated with BNCT (n=21) had a median survival time (MST) of 15.6 months (95% confidence interval (CI): 12.2-23. 9) after diagnosis. The major difference between this study and the present study is the neutron source. While this study is a clinical trial using an accelerator for medical device approval, OSAKA-TRIBRAIN0902 is clinical research using a nuclear reactor, which cannot be considered a medical device under the regulations. In Japan, If I had to choose a word, clinical studies required for the approval of medical devices and drugs are so-called clinical trials. Those that do not aim to obtain data for application for approval are clinical research.

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Keywords: glioblastoma, clinical trial, phase1,

Operation of BNCT clinic in Korea

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In the past, Korea conducted basic research on Boron Neutron Capture Therapy (BNCT) using a reactor. However, for practical patient treatment, it was necessary to develop a medical device based on an accelerator for BNCT that can be installed within a hospital. Since 2016, DAWONSYS Co., Ltd. and its medical subsidiary, DAWONMEDAX Co., Ltd., have developed a complete solution for BNCT systems based on a linear proton accelerator system and boronophenylanine capable of treatment. This is the first instance of comprehensive commercialization development in Korea, which includes large-scale radiotherapy equipment, pharmaceuticals, treatment planning systems, medical techniques, and quality inspection and testing methods.
BNCT is a highly collaborative field that requires the expertise of various professionals. In the challenging domestic medical development environment, it represents a convergence of technology outcomes from industry, academia, research, healthcare, and government. DAWONMEDAX Co., Ltd. has installed an A-BNCT system (10MeV, 2mA) at Songdo in Incheon, which is operational for research purposes. The A-BNCT Center was unable to conduct clinical trials due to specific legal regulations in Korea. As the first proactive administration, we established a remote BNCT clinic to support clinical trials through collaboration. The BNCT clinic is expected to conclude its role once clinical trials are completed.
In addition, clinical trial plans for recurrent high-grade glioma of BNCT have been approved through deliberation with domestic regulatory authorities such as the Ministry of Food and Drug Safety and the Ministry of Health and Welfare. As of December 2023, eleven patients have received treatment, including six with clinical trials and five under compassionate use. The clinical trial institutions include Gachon University Gil Medical Center, the National Cancer Center, and Seoul St. Mary's Hospital. Clinical trials for head and neck cancers have also been approved and are scheduled to be conducted in 2023, with the addition of Seoul National University Hospital. The BNCT clinic has established an emergency response system for patients as a remote hospital for clinical trials. It ensures the safe management and operation of pharmaceuticals and medical devices. As the first BNCT facility in Korea, it strictly enforces radiation safety management, providing a secure radiation facility for both patients and medical staff. We experienced a very challenging environment to develop and introduce new medical systems and have overcome adversity. We hope that our example will be helpful to you.

Keywords: Korea, A-BNCT, clinic, operation

Impact of liver dose reduction in BNCT using LiF collimator: treatment planning aspect

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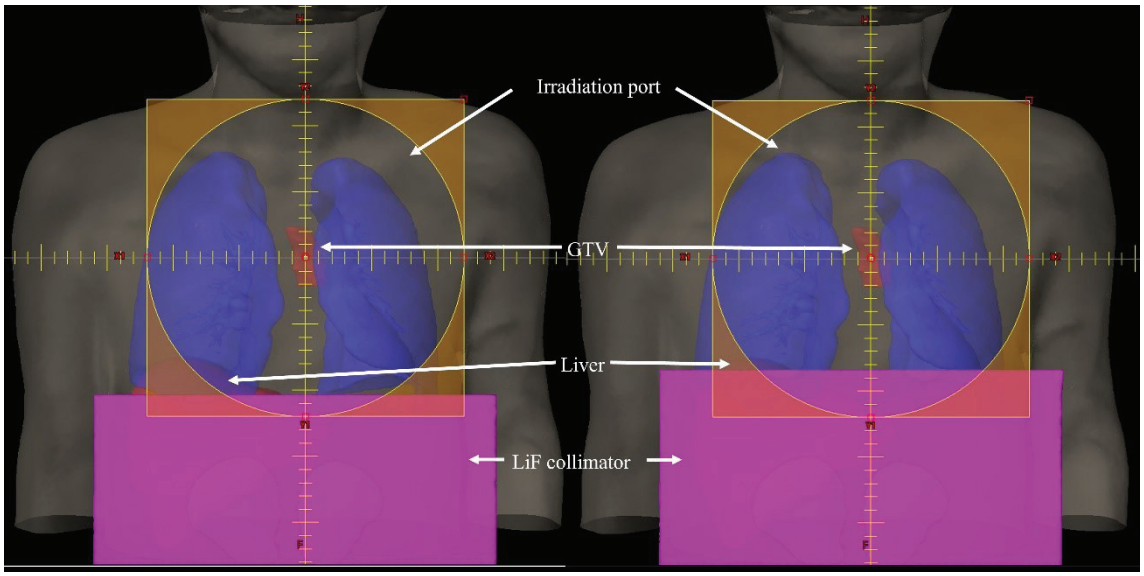

Figure captions: Beam's eye view of plan C1 (left) and plan C2(right). The beam direction was anterior-posterior.

[Purpose] The accelerator-based boron neutron capture therapy (BNCT) for locally advanced or recurrent head and neck cancers is covered by insurance in Japan. Furthermore, using another accelerator-based BNCT system, CICS-1 (manufactured by Cancer Intelligence Care Systems, Inc.), a phase II clinical trial for angiosarcoma is being conducted at the National Cancer Center Hospital, Tokyo, Japan (NCCH). CICS-1 has a 24 cm diameter irradiation field. It may cause increased doses of organs at risk (OARs) around the tumor. This study evaluated the effect of dose reduction by ^{6}LiF collimator on the treatment planning for a thoracic tumor in BNCT.

[Materials & Methods] The collimator manufactured by Nikkei Sangyo Co., Ltd. was made of ^{6}LiF, which had a large cross-section of ^{6}Li(n,t)^{4}He reaction in the energy of the thermal neutron. The collimator thickness and the density were 5 mm and 2.3 g/cm^{3}, respectively. The size of the collimator was assigned to cover the whole liver's size. A patient with thoracic esophageal cancer who received radiotherapy in NCCH was enrolled in this study. RBE-weighted equivalent dose distribution in this patient was calculated by CT images via a Monte Carlo simulation code (PHITS, ver. 3.02). Since the treatment plans were assumed to be the two-fraction treatment and 2 different beam angles (Anterior-Posterior and Posterior-Anterior directions), only one beam angle was used per the treatments. To compare the treatment plan with and without the ^{6}LiF collimator, three treatment

plans (without the collimator: 1 (original plan), with the collimator: 2 (plan C1 and C2)) were calculated to evaluate whether the dose reduction in the liver was expected. The distance between the lower edge of gross tumor volume (GTV) and the upper edge of the collimator was changed in plan C1 and C2 (Figure 1). The equivalent dose of GTV and OARs (liver and oral mucosa) was evaluated by prescribing the maximum dose (Dmax) of 18 Gy-Eq to the skin. In this study, compound biological effectiveness (CBE) of the tumor, liver, oral mucosa, and skin were 4.0, 4.25, 4.9, and 2.5, respectively. In addition, considering the tolerance dose of each OAR, the equivalent doses of GTV and OARs were also evaluated when prescribing the mean dose (Dmean) of 5.0 Gy-Eq[1] to the liver. MIM maestro (ver. 7.2.7, MIM Software Inc.) was used to evaluate the equivalent dose distribution.

[Results & Discussion] In prescribing the Dmax of 18 Gy-Eq to the skin, the minimum dose (Dmin) of GTV for the original plan, plan C1, and plan C2 were 54.1, 50.6, and 50.2 Gy-Eq, respectively. Then, the Dmean of the liver were 10.5, 8.53, and 8.27 Gy-Eq, respectively. Furthermore, The Dmax of the oral mucosa were 19.0, 15.2, and 15.2 Gy-Eq, respectively. When the dose prescription was changed with the Dmean of 5 Gy-Eq to the liver[1], the Dmin of GTV for the original plan, plan C1, and plan C2 were 25.7, 29.6, and 30.3 Gy-Eq, respectively. Then, the Dmax of oral mucosa were 9.01, 8.93, and 9.24 Gy-Eq, respectively. Whichever dose prescription was performed for each plan, Dmin of GTV converted to the equivalent dose in 2 Gy fraction (EQD2, α/β = 10 Gy) exceeded 50 Gy-Eq (50.5-153.8), which the dose corresponded to the single fraction dose of 20 Gy[2]. Using the collimator increased the minimum tumor dose by achieving the dose constraints of the OARs.

[Conclusion] This study investigated the effectiveness of the ^{6}LiF collimator for BNCT. It was shown that with appropriate use of the ^{6}LiF collimator, it may be possible to deliver a sufficient dose to the tumor while lowering the doses to OARs.

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Keywords: Accelerator-based BNCT, Treatment planning, esophageal

Current Status of BNCT for FDS Consortium

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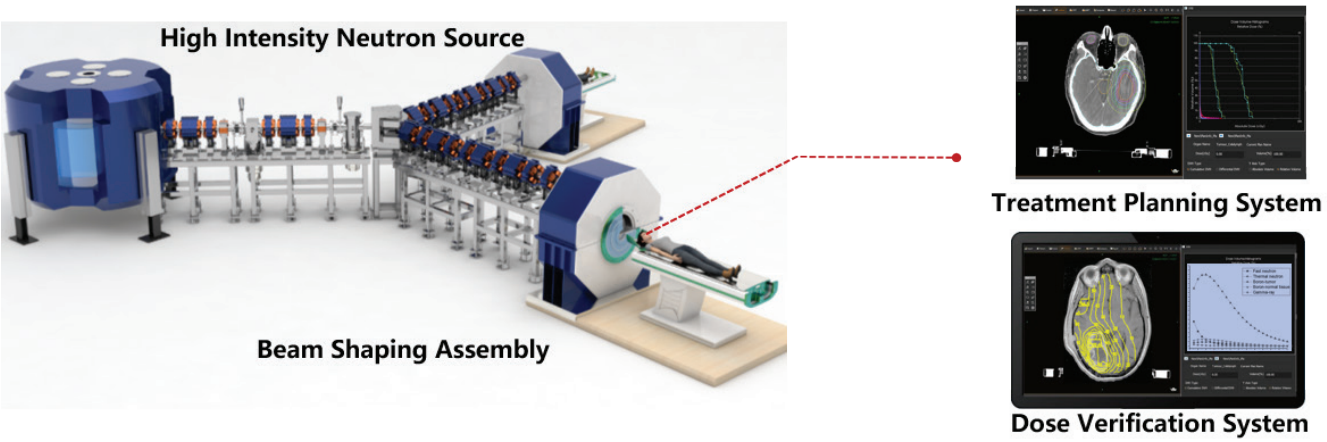

Figure captions: Main components of Accurate Neutron Therapy System (NeuKnife)

Boron neutron capture therapy (BNCT) an epoch-making cancer treatment, which selectively destroys cancer cells without serious damage to normal cells. This method is obviously the most effective approach to tumor with high malignancy, such as in brain tumors, in which healthy and tumor cells coexist as an intermingled form. The neutron can easily passes through the tissues and almost does not negatively affect the body, and it causes nuclear reaction if boron compound exists within the cancer cells. The nuclear reaction implies the reaction of alpha beams and lithium particles, which have cell-level accuracy. BNCT is 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 consortium has developed the Accurate Neutron Therapy System (NeuKnife™), with world leading level parameters and advantages of short treatment time, high treatment accuracy (cell level), high level safety. NeuKnife™ owns several key features in the design: (1) High Intensity Neutron Source: Miniaturization accelerator neutron source design with inherent safety. (2) Beam Shaping Assembly: Adjust neutron energy and spectrum and ensure the curative effect. (3)Treatment Planning System: Dedicated treatment plan design according to the patient. (4) Dose Verification System: Improving therapeutic effect through dosimetric optimization.
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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Regulatory aspect of the beam quality of the neutron irradiation systems for boron neutron capture therapy

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A first-in-the-world accelerator-based neutron irradiation system was approved for boron neutron capture therapy (BNCT) for advanced and recurrent head and neck cancers by the Japanese regulatory authority, Pharmaceuticals and Medical Devices Agency (PMDA), in 2020 after a clinical trial in Japan. However, several study groups in Japan are developing new accelerator-based neutron irradiation systems for BNCT. They have to conduct clinical trials to obtain regulatory approval for BNCT even for advanced and recurrent head and neck cancers because the equivalency of neutron beam quality is not approved among the neutron irradiation systems under development in the regulatory circumstances of Japan. However, if the regulatory authorities find that the equivalency of the neutron beams among manufacturers, regulatory approval of the neutron irradiation systems may be obtained without the time-consuming and expensive steps of clinical trials. International Atomic Energy Agency published a book, Advances in Boron Neutron Capture Therapy, which comprehensively reports on the current state of the science and the supporting technology for accelerator-based neutron sources for BNCT in 2023. It was written to offer practical guidance in decision-making for the neutron sources for BNCT but does not offer information on the biological and clinical equivalency of the neutron beam. The Japanese Society for Neutron Capture Therapy established the Neutron Beam Characterization Guidelines Committee in 2021 and initiated a project to develop guidelines for the range and conditions under which neutron beam quality can be considered substantially equivalent from physical, biological, and clinical perspectives. This project has also been financially supported by the Japanese Agency for Medical Research and Development (AMED) since July 2023 and aims to establish guidelines for neutron beam characterization that will be approved by the Japanese Society for Neutron capture Therapy. The regulatory authorities might refer to these guidelines when conducting a medical device affairs review of neutron irradiation systems, by which we expect a simpler and faster review process. In this presentation, the activities of the Neutron Beam Characterization Guideline Committee and an outline of the guidelines for neutron beam characterization to be developed in the future will be explained.

Keywords: Beam quality, equivalency, regulatory approval

Requirements for a suitable Japanese medical care provision system and its personnel in boron neutron capture therapy

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Purpose: Boron neutron capture therapy (BNCT) using the accelerator-based neutron irradiation system (NeuCure®, Sumitomo Heavy Industries, Ltd.) and the boron drug (Steboronine®, Stella Pharma Corporation) have been covered by insurance treatment for recurrent or locally advanced head and neck cancer in Japan since 2020. Furthermore, another neutron irradiation system (CICS-1, Cancer Intelligence Care Systems, Inc.) and the same boron drug for which a Phase II clinical trial are being conducted for angiosarcoma have been designated as orphan medical device and drug for rare diseases in Japan, respectively, and the accelerator-based BNCT is expected to become widespread. BNCT requires a high level of specialization of medical staff, as well as human resource development and appropriate allocation, and consolidation. However, no data exists to estimate the appropriate balance between regional unevenness and demand. It is necessary to reveal the current situation regarding the implementation status, the number of treated patients, the waiting list status, and the medical staff resources. This study conducted a questionnaire survey of the workload and the ability of each profession to discuss them. Methods: From August to September 2023, the questionnaire surveyed items related to the implementation status, the number of treated patients, the uneven regional distribution of treated patients, the waiting list status, and the average working hours in each of the professions engaged in BNCT. The institutional review board of the National Cancer Center Hospital, Tokyo, Japan, approved this study.

Results: Responses were obtained from 12 physicians (MDs), 13 medical physicists (MPs), and 7 radiological technologists (RTs) belonging to 3 medical institutions performing BNCT for the patients in Japan. The MDs engaged in BNCT came from diverse backgrounds, and a wide variation was observed in their working hours and primary tasks. Furthermore, there were no established standard quality control (QC) and quality assurance (QA) methods, and the content of QC and QA varied among the facilities. Even MPs and RTs engaged in BNCT, they do not necessarily have the sufficient knowledge and skills to handle all QC and QA works related to BNCT. In addition, even if MP and RT had long experience in conventional radiotherapy, such as X-ray therapy, MP and RT with no experience in BNCT were almost impossible to perform BNCT-specific works. All of the facilities received many inquiries from in and out of the prefectures about the eligibility of BNCT, and only 6-21% of the patients referred to BNCT received it among the institutions. The median time of the required working hours for a patient treatment was 52.6 h (MD + registered nurse: 11.3 h, MP: 30.3 h, RT: 11.0 h). Considering the working hours for the decision of BNCT indication including ineligible patients, it reached almost 1.3 times longer than them. It also became clear that the burden on staff for work other than actually performing BNCT was extremely high.

Conclusion: This study collected the fundamental data to achieve a suitable Japanese medical care provision system and its personnel in BNCT. BNCT is a new radiotherapy that requires highly specialized knowledge and skills. Hence, the training of MDs, MPs, and RTs with sufficient skills and knowledge to understand and appropriately perform BNCT-specific works and the standardization of the content of QC and QA works are urgent issues. In addition, the number of facilities performing BNCT was limited, and patients were concentrated in and out of the prefectures to perform BNCT, suggesting that potential demand was not being met. In the future, it will be necessary to fully grasp such potential demand while making it possible to operate the BNCT system efficiently based on our data.

Keywords: BNCT; Workload survey; Staffs' capability

Current status of Helsinki University Hospital BNCT facility

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Boron Neutron Capture Therapy (BNCT) is a biologically guided radiotherapy method developed to treat patients with malignant tumors using an epithermal neutron beam. The Helsinki University Hospital will start BNCT treatments in the near future using a compact accelerator-based neutron source manufactured by Neutron Therapeutics Inc. The system is a single ended electrostatic proton accelerator, where neutrons are generated in a solid lithium target with the reaction ^{7}Li(p,n)^{7}Be. The accelerator is located at the hospital campus, where all hospital infrastructure is available. The safety and efficacy of the L-boronophenylalanine-fructose (BPA-F)-mediated BNCT have previously been evaluated in clinical trials in patients with head and neck carcinoma or malignant glioma at the Finnish BNCT facility located at the FiR 1 research reactor [1].
Commissioning of the accelerator-based BNCT facility started in 2018, and the facility design meets applicable standards for a radiotherapy unit. The nuBeam treatment suite includes a CT image-guided robotic patient positioning system, and a treatment-planning software with a Monte Carlo based dose engine. The facility is equipped with a laboratory for neutron dosimetry and for boron analysis. The Radiation Safety Authority of Finland has approved the usage of the facility for neutron beam commissioning [2].
The neutron beam has been characterized using neutron activation analysis and a paired ionization chamber technique. The measurements confirmed that the beam properties fulfill the criteria for a BNCT neutron source as described in TECDOC of the IAEA [3]. The radiation dose rate is measured routinely after the beam delivery in the treatment room. These measurements confirmed a low activation level with a fast decay rate allowing the personnel to enter the room shortly after the end of neutron irradiation. Commissioning of the facility is now at the final stage, including verification and validation of the treatment planning system and end-to-end testing of the patient treatment workflow. Once the commissioning is complete and approval by the national authorities has been obtained, the first clinical trial will be initiated on patients with inoperable, locally recurrent head and neck cancer.

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Granada Project NeMeSis for an accelerator-based facility for BNCT: simulations of treatment of patients of brain tumors of bad prognosis.

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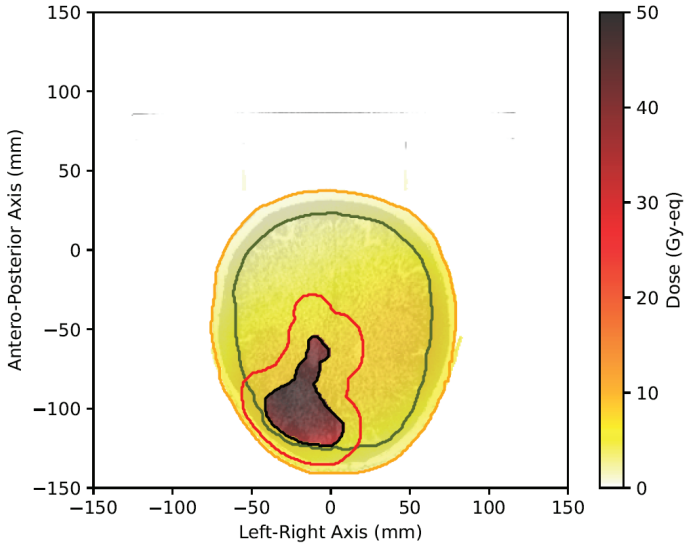

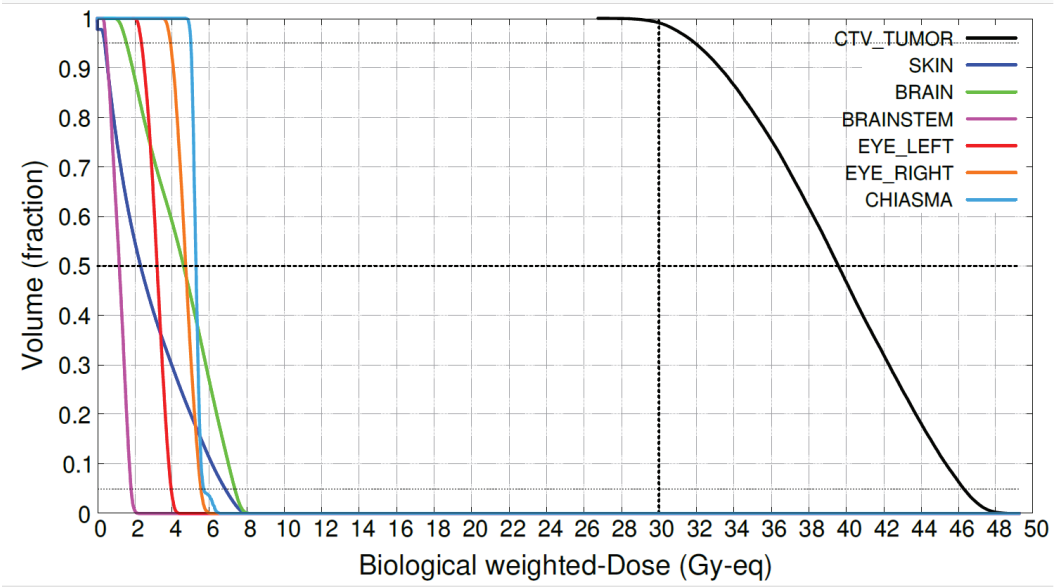

Figure captions:
Fig. 1. Dose map of the BNCT therapy with the contours of the CTV (black curve) and the PTV (red line) of conventional radiotherapy.
Fig 2. Dose-volume histogram for the proposed BNCT treatment.

Purpose/Objective: Boron Neutron Capture Therapy (BNCT), a form of radiotherapy that is selective at cellular level, is facing a new era with the development of accelerator-based neutron sources that can be place in hospitals [1]. The project NeMeSis

(Neutrons for Medicine and Sciences) of the University of Granada and the Hospital Virgen de las Nieves [2] proposes a facility for BNCT with an optimal neutron source for this therapy, removing completely the more undesirable fast neutrons on the beam [3].

Material/Methods: The neutron beam would be obtained from 2.1 MeV protons onto a lithium target at 30 mA of current, possible at present with available accelerators. The produced neutron field is determined throughout analytical descriptions of experimental data of the well-known proton on lithium reaction near the threshold. Then, a Monte Carlo simulation of the neutron moderation and collimation in a specially designed beam shaping assembly (BSA) is done with MCNP 6.2. The BSA is mainly composed of MgF_2 with Pb reflectors, thermal neutrons and gamma filters of different materials. The beam is studied by depth dose profiles in tissues and simulations of treatment of patients with GBM using their DICOM data from their medical images. The whole body radiation dose is estimated with anthropomorphic phantoms. For simulations of patient treatment, we use a standard 3.5 ratio difference in concentration of boron (tumor/ normal brain tissue) as an average value found in clinical trials. Overall treatment is normalized for a maximum dose of 8 Gy-eq in 1 cc of brain, and a CVT dose >30 Gy-eq for a single session.

Results: The features of the beam at the exit port accomplished all recommendations from the IAEA for BNCT. The results for the simulation of patient treatment shows the performance of the neutron source, allowing therapeutic doses at the CTV in a single session while maintaining all organs at risk well below the tolerable limits, even when the tumor is located next to critical organs such as optical nerves and chiasma (Fig. 1 and 2). Moreover, the effective whole-body dose received by the patient is estimated below 60 mSv, a quantity that is comparable to other forms of radiotherapy.

Conclusion: The accelerator-based neutron source projected at NeMeSis can feasibly be applied to the treatment of brain tumors of bad prognosis.

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Keywords: BNCT, neutron source, DVH

Present status of NECTAR project to ascertain the feasibility, safety and effectiveness of low dose and low dose rate NCT in the treatment of Alzheimer's disease

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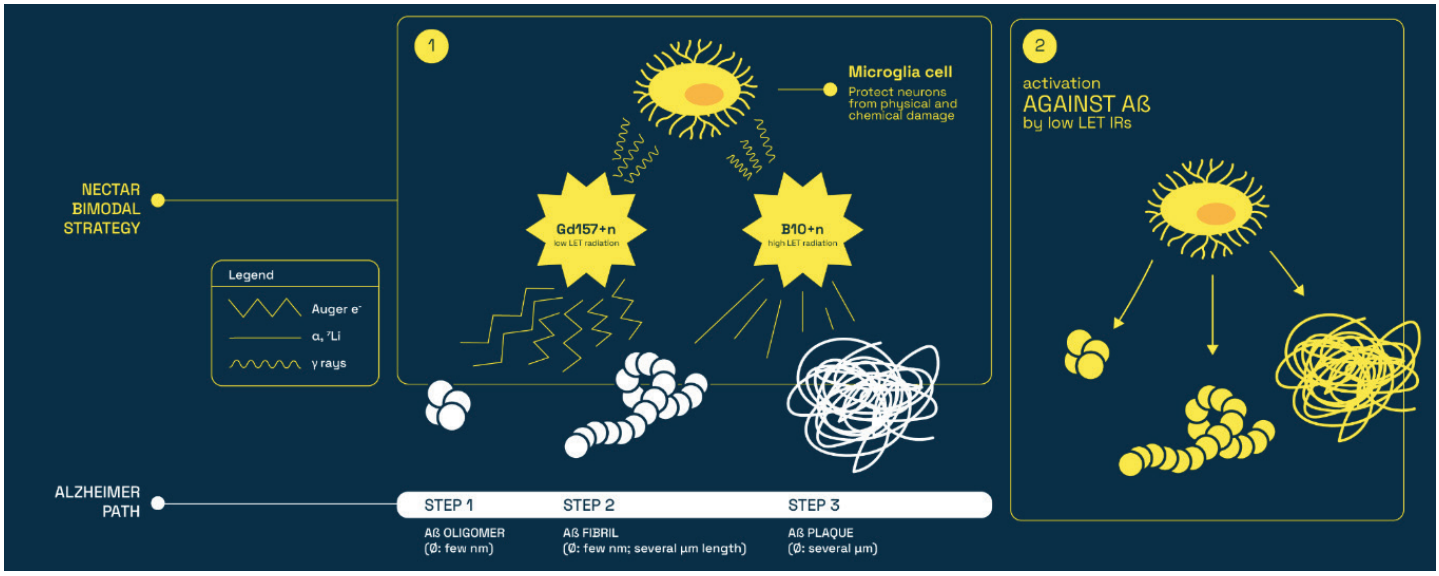

Figure captions: The bimodal treatment under investigation by NECTAR and addressing the different stages of aggregation of the beta-amyloid protein of AD

Neutron Capture Therapy (NCT), since its first theoretical hypothesis [1], was applied mainly as a cancer treatment with limited studies regarding other diseases [2,3]. As cancer treatment, it is actually more correct to speak of BNCT being B10 almost the sole nuclide in clinical use and under investigation for future NCT agents. The isotope 157 of Gadolinium (Gd157) aroused the interest of the scientific community since a while [4]. The extremely short ranges of the charged secondaries (internal conversion and Auger electrons) set a very strong constraint on the GdNCT agent localisation inside the targeted cell which must bind DNA molecule directly. Nonetheless, the clinical use of Gd-enriched compounds as MRI-probes supports the current interest in GdNCT [5].
Alzheimer's disease (AD) is the most common form of dementia (50-60% of all cases) [6]. Currently over 55 million people worldwide live with dementia and the number is expected to rise up to 139 million by 2050. Statistics say a new case of dementia arise somewhere in the world every 3 seconds. AD destroys nerve cells thus limiting or abolishing higher brain functions (memory, mobility, behaviour...). In the most advanced stages, patients are unable to care for themselves and need constant help in their daily life. This means huge costs, economically and psychologically, and indeed if we consider dementia as a country it would be the 14th largest economy worldwide, with a US$ 1.3 trillion current cost. Despite the ongoing debate on AD pathogenesis, still the central role of the misfolded beta amyloid protein (Aβ) is widely accepted. In particular, studies [7] identified the oligomers, one of the first stages of aggregation of Aβ, as the most neurotoxic species. In the late 1990's, the effectiveness of conventional radiotherapy in the treatment of TracheoBronchial Amyloidosis (TBA) suggested the idea of a possible beneficial effect of photon irradiation in AD as well [8,9]. Presently, evidences are under collection to demonstrate preclinically and in very small patient's cohorts the feasibility of such treatment [10-12].
In this scenario, the H2020 project "NECTAR": NEutron Capture enhanced Treatment of neurotoxic Amyloid aggRegates, headed by the Physics Department of Pavia University and exploiting an EU-based consortium including academic and non

academic partners, aims to investigate the feasibility, safety and effectiveness of low energy neutron irradiation of the whole brain affected by AD in combination with the neutron capture reactions on B10 and Gd157.
Indeed, and thanks to the match between the Aβ aggregates dimensions and the ranges of B10 and Gd157 charged secondarie, a local depolymerisation of the aggregates is hypothezised. In parallel, the glia cell compartment of brain is supposed to be stimulated by the highly penetrating photons emitted by the very same capture reactions and so promoting the clearance of the Aβ debris, as already observed by the extension of conventional radiotherapy to AD. NECTAR will be the proof of concept at the preclinical stage of a bimodal treatment for AD capable of being sensitive to all the phases of aggregations of Aβ thanks to the development of specific new molecules designed to selectively bind Aβ protein. Due to the progressive and chronic features of AD, the effectiveness of a treatment using highly fractionated irradiation protocols based on low doses and low dose rates per fraction must be pursued as well. The available evidences of a positive effect of LDIR (low dose ionising radiation) in the brain [13] is an important scientific background in this sense. The presentation deals with a brief overview of the NECTAR project and then with a roundup of the most recent achievements.

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A new Boron Neutron Capture Therapy clinical centre in Italy: technological innovation and improved methods from the neutron beam to the patient dosimetry

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**G. Paolisso and V. Vercesi are the Principal Investigators of the BNCT project described in this article*

A Boron Neutron Capture Therapy (BNCT) research and clinical centre will be installed in Caserta, in the south of Italy, funded by the National Complementary Plan to the National Recovery and Resilience Plan, PNC-PNRR, within the project named ANTHEM (Advanced Technologies for Human-Centred Medicine) and by the University of Campania Luigi Vanvitelli. The new BNCT infrastructure is based on the technology developed by the Italian National Institute for Nuclear Physics (INFN) to produce an intense neutron beam starting from a radiofrequency quadrupole accelerator able to deliver a 5 MeV, 30 mA proton beam, coupled to a beryllium target and to a *beam shaping assembly* for neutron moderation and collimation. This technology will be the core of a centre that will serve as a hub for BNCT research and for the treatment of tumours that have poor response to other therapies or do not have any other therapeutical indication, such as, for example, Glioblastoma Multiforme. The design of the building and the project for the implementation of the necessary activities such as boron measurements, radiobiology studies, imaging, treatment planning have recently started, stemming from the long experience of BNCT research carried out in Italy together with different international collaborations. *The aim is to promote a global innovation in BNCT, by integrating different aspects that are normally tackled separately.* The vision is to exploit the knowledge generated in basic research and in technology development in a more structured way. BNCT is a complex field, where the effectiveness of the treatment depends on the interplay among various factors, including the physical quality of the beam, the radiobiological response of the irradiated tissue, and the specificity of the treatment planning. While the final details of the accelerator and target construction are being defined, work is ongoing to optimise the neutron beam characteristics using meaningful clinical figures of merit, to implement more refined dosimetry methods, able to predict clinical results obtained in former trials, and to produce new radiobiological data to better understand the dose-effect relationship in BNCT. The incorporation of these data into models for photon-equivalent dose calculation and treatment planning software enables more personalised and precise in-patient dosimetry, representing a significant step towards a new clinical reality in Italy. This contribution shows some details of the latest advancements, highlighting the progress made towards achieving this goal and the status of the centre design.

Keywords: clinical centre, dosimetry, neutron beam

Ureidosulfamido ortho-Carboranes as the key to combine BNCT with Carbonic Anhydrase Inhibition for Mesothelioma Treatment

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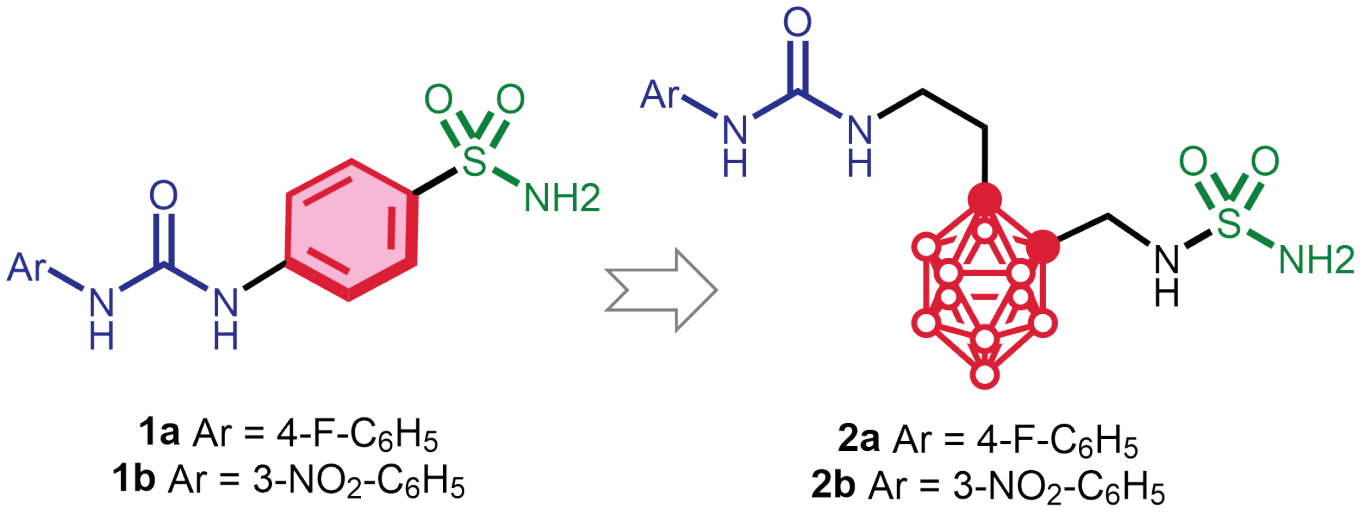

Figure captions:
Figure 1. Structures of CA IX inhibitors 1a-b and our boronated analogues CA-USFs

Carbonic Anhydrases (CAs) belong to a family of metalloenzymes that catalyse the reversible hydration of CO_2 to release HCO_3^- and H^+, and favour the spreading of the cancer by maintaining the pH of the extracellular environment. CA IX is over-expressed in several tumours, including pleural mesothelioma. In this context, sulfamidic scaffolds showed exceptional inhibition against CA, however a certain selectivity is required. Compounds **1a-b** revealed to be potent and selective CA IX inhibitors.[1]
Closo-carboranes behave as 3D-bioisosteres of aromatic rings thanks to the volume of the cage and their pseudo-aromaticity. They possess a high boron content thus being excellent boron delivery agents in Boron Neutron Capture Therapy (BNCT).[2] In this work, we present the synthesis of ureido-sulfamido-carboranes **CA-USFs** and their application in mesothelioma treatment exploiting a synergistic combination of BNCT and CA IX inhibition. A straightforward orthogonally protected o-carborane intermediate has been designed to obtain **CA-USFs** in eleven steps and satisfying yields. CA II and CA IX inhibition was firstly studied, and it was confirmed that the introduction of a fluorine or nitro group on the aromatic ring is fundamental to improve the inhibition of both enzymes. Moreover, a higher inhibition of CA IX esterase activity with respect to the ubiquitous CA II was evidenced. In order to carry out *in-vitro* and *in-vivo* BNCT experiments, ^{10}**B F-CA-USF** and ^{10}**B NO_2-CA-USF** were prepared and tested on AB22 (murine) and ZL34 (human) mesothelioma cells. The boron uptake was then determined and it was sufficient for a BNCT treatment. *In-vitro* studies evidenced a complete hamper of cell proliferation, especially for **NO_2-CA-USF**. Moreover, treated mice tumour showed a size reduction compared to un-treated control mice with a significant higher effect in combination with BNCT. Finally, **CA-USFs** demonstrated to be *in vivo* well tolerated at a therapeutic dose, thanks to their administration as inclusion complexes of β-CD (cyclodextrins).

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Synthesis and characterization of B4C-based multifunctional nanoparticles for BNCT Applications

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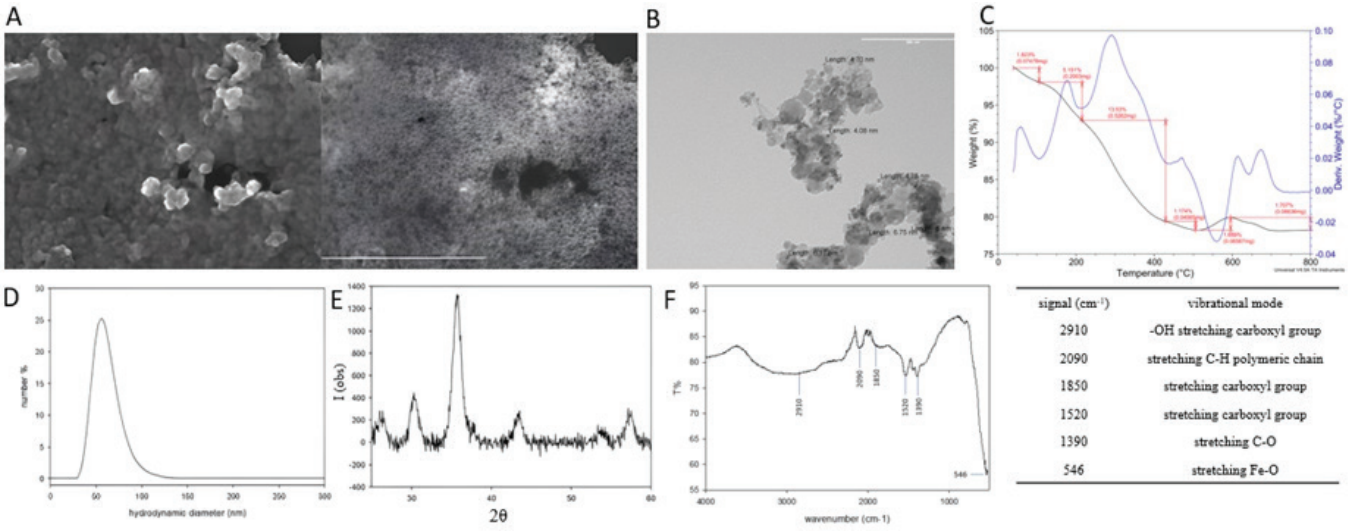

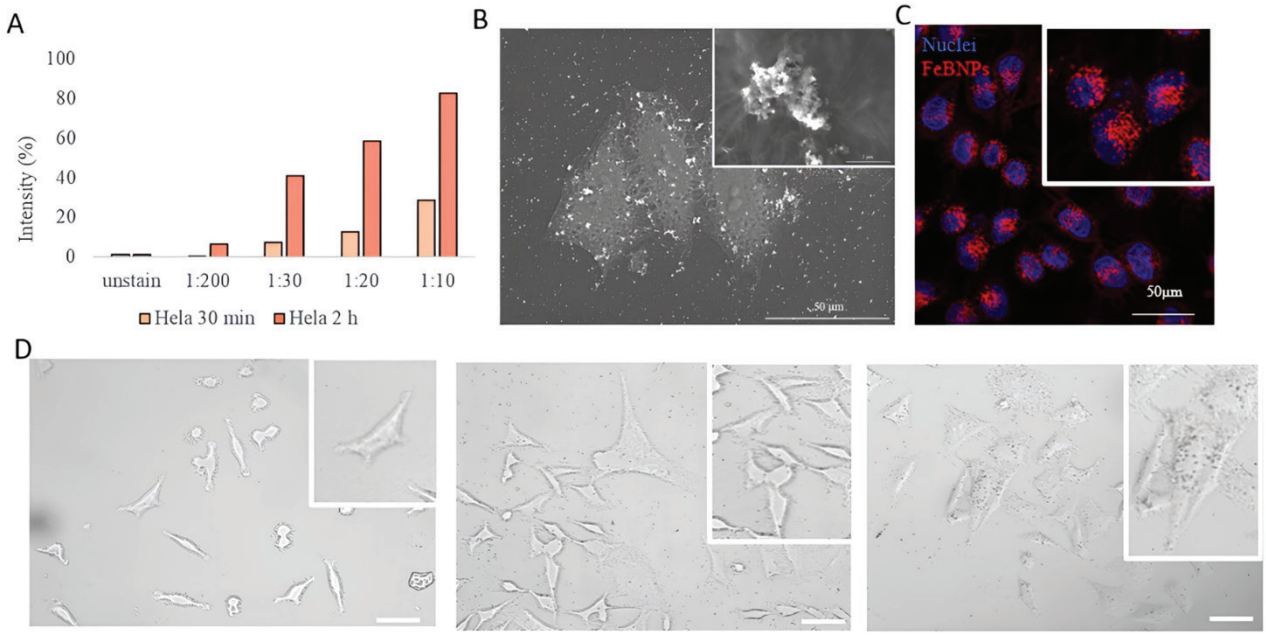

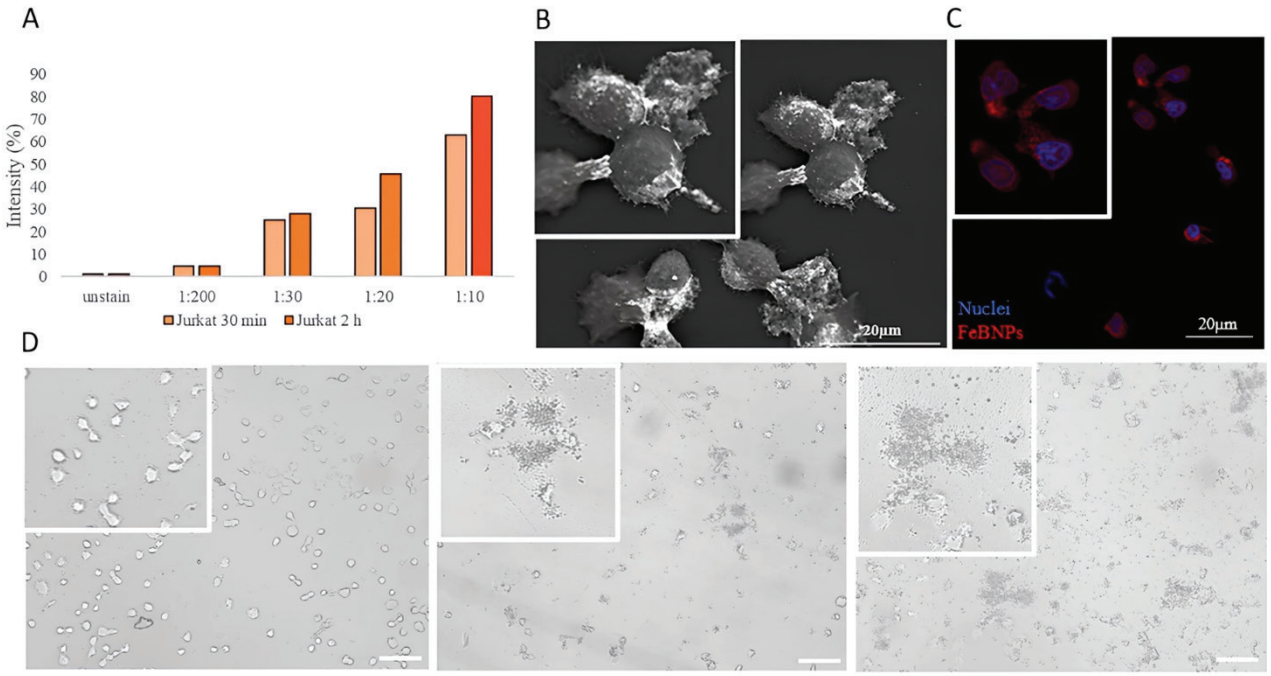

Figure captions:
Figure 1. Nanoparticles characterization
Figure 2. Evaluation of Nanoparticles' interaction with HeLa cells
Figure 3. Evaluation of Nanoparticles' interaction with Jurkat cells

The use of nanomaterials stands out as a promising frontier in the advancement of Boron Neutron Capture Therapy (BNCT) applications. Nanocarriers, including liposomes, micelles, and dendrimers, offer the advantage of encapsulating a high payload of boron compounds and facilitating their selective delivery to tumours. However, the aforementioned structures could undergo changes in structure and stability in physiological conditions, leading to premature release of boron compounds before reaching the tumour site[1]. On the other hand, inorganic boron compounds can offer great stability under various physiological conditions. Moreover, nanoparticles of inorganic boron compounds offer the opportunity to achieve high localised concentrations of ^{10}B, resulting in prolonged retention times within the organism[2]. Boron carbide (B_4C) emerges as particularly noteworthy due to its high volumetric concentration of boron atoms, comparable to elemental boron, potentially avoiding the need for isotopic enrichment in ^{10}B. Furthermore, boron carbide exhibits exceptional chemical inertness and high biocompatibility[3]. B_4C NPs have already been investigated as possible ^{10}B carriers for BNCT [4]. The primary challenge associated with the use of B_4C NPs lies in its inherent hydrophobicity and low reactivity, posing obstacles to achieving effective chemical functionalization. Furthermore, due to the low atomic weight of the component atoms, B_4C NPs are difficult to detect and quantify once they interact with biological systems. In this work, we present the synthesis of complex multifunctional composite nanomaterials obtained through the co-localization of B_4C, as ^{10}B carrier, with an MRI active moiety, represented by superparamagnetic iron oxide nanoparticles (SPIONs), and an optical fluorophore. This complex nanostructure will offer the possibility not only to exploit the BNCT therapeutic effect of a high-density boron carrier but also to monitor its distribution in tissues and at the cellular level. The water stability of these nanostructures (FeBNPs) is obtained through functionalization with poly(acrylic)acid (PAA), allowing a further functionalization with the fluorophore DiIC18(3). FeBNPs underwent characterization of their size, morphology, and ^{10}B content. Subsequent in vitro investigations were conducted to assess their interaction with both HeLa and Jurkat cell lines, examining their biocompatibility and extent of engagement with biological systems. The nanoparticles' potential as a Boron Neutron Capture Therapy (BNCT) agent was evaluated through a combination of imaging techniques, including confocal, scanning and transmission electron microscopy. Additionally, micro-distribution studies were conducted using intracellular neutron autoradiography, providing valuable insights into the nanoparticles' spatial distribution within cells and the overall cell population. These findings strongly indicate that the developed nanomaterials hold significant promise as effective carriers for ^{10}B in BNCT, showcasing their potential for advancing cancer treatment methodologies.

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Keywords: boron carriers, nanoparticles, neutron autoradiography

Which boron cluster is best for BNCT?

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Since many decades, boron clusters (polyhedral compounds consisting of – mostly – boron atoms) have attracted interest as carriers for BNCT. To date, only one compound (BSH, $[B_{12}H_{11}SH]^{2-}$) has been used clinically. In this overview, the properties (chemical, physical, biological) of the different cluster compounds are presented and their advantages and drawbacks are reviewed.
Boron clusters are usually attached to organic building blocks which convey a targeting of the desired compound. Therefore, the chemistry of boron clusters is important. Furthermore, they have properties in their own right, which may enhance or reduce the targeting principle. They may also have targeting principles in their own right, and then hybrid molecules might not be suitable. One should remember that BNCT relies on the presence of rather large concentrations of boron for being effective. Therefore, toxicity as well as water solubility or the introduction of transport excipients must be considered.
Neutral boron clusters (in BNCT, the three different isomers of dicarba-closo-dodecaborane are used) offer a facile chemistry and can be connected freely to other organic building blocks. They are among the most hydrophobic building blocks known, which makes them rather water-insoluble. In addition, the 1,2-dicarbadodecaborane (o-carborane) is easily attacked by bases also in physiological settings.
Charged boron clusters (most widely investigated are the degradation product of o-carborane, $[B_{12}H_{12}]^{2-}$, $[B_{10}H_{10}]^{2-}$ (also known as GB10), and metallacarboranes) possess higher water solubility. Nevertheless, as all of these clusters are supercha-otropic ions, they have properties which might influence the targeting principles of the organic moiety. For $[B_{12}H_{12}]^{2-}$, recent advances in chemistry has opened the avenue to attach this cluster easily to organics. For metallacarboranes, the chemistry is less versatile. For $[B_{10}H_{10}]^{2-}$, conjugation is even less developed, and is further hampered by the presence of two different types of boron atoms. In conclusion, the presently available boron clusters all have drawbacks for use in BNCT.

Keywords: boron cluster, targeting, chemical synthesis

Neutron autoradiography and UV-C sensitization reveals intracellular boron microdistribution in HER2+ breast cancer cells after liposomal boron delivery

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The measurement of boron concentration distribution is a key aspect of BNCT. Moreover, the short range of high-LET particles from boron neutron capture (BNC) reactions leads to highly localized energy deposition, and consequently, the spatial microdistribution of boron is a relevant factor in the energy deposition distribution. In previous work, our group developed a protocol that combines neutron autoradiography and UV-C sensitization to improve the spatial resolution of nuclear track detection from BNC reaction products in biological samples, without the need for complex digital imaging co-registration techniques. This method has broadened the potential for measuring intracellular boron microdistribution concentration, enabling detailed comparisons of boron compound uptake and distribution profiles while offering potential applications in the field of microdosimetry. In this work, we present the results concerning the boron intracellular microdistribution achieved by boron-containing liposomes in a breast cancer cell line, contributing to the research efforts of the ongoing project evaluating BNCT with inmunoliposomes for HER2+ breast cancer treatment in Argentina (Gadan et al., 2015). Liposomes housing two boron compounds, LCOB and GB-10, were sinthesized by means of microfluidic technology using a micromixer device developed at CNEA, and characterized in terms of size distribution using Dynamic Light Scattering (DLS) technique while boron and phosphorous concentration measurements were performed in an ICP-OES equipment. In order to assess the boron microdistribution, the former established protocol of neutron autoradiography combined with UVC sensitization (Gadan et al., 2019) was succesfully applied in SKBR-3 cells, a human breast cancer cell line chosen for its suitability for HER2+ cancer subtype studies. Briefly, according to this protocol, cells were seeded on polycarbonate detector foils and incubated with a liposomal culture medium solution at different established incubation times (6, 24 and 48 h). Following, cells were washed and fixed. In order to produce light ion tracks coming from BNC reaction, foils were irradiated under a thermal neutron fluence. After irradiation, cells were stained with haematoxylin and exposed to UV-C for cells imprints formation and a chemical etching process using PEW was applied. Images were acquired using an optical microscope coupled to a CCD camera. For cell structure segmentation, an in-house computational code developed in Matlab was applied together with a process based on arithmetical operations to classify and count tracks located both in nucleus or cytoplasm cell compartments.
Microfluidic technology successfully encapsulated boron compounds in liposomes, demonstrating its versatility compared to traditional fabrication methods. The experimental results revealed the effective incorporation of boron-containing liposomes into the SKBR-3 cells. Combining neutron autoradiography and UV-C sensitization, we measured boron microdistribution across the nucleus and cytoplasm at different incubation times. This work represents an advance in our research line aimed at developing inmunoliposomes for the BNCT treatment of HER2+ breast cancer. The methodology and analysis can be applied to other types of cancer cell line models and boron compounds, and it allows for accurate microdosimetry calculations with application in radiobiological models

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Keywords: liposomes, neutron autoradiography, boron microdistribution

Synthesis and preliminary evaluation of boronated glucosamine derivatives as boron carriers for BNCT

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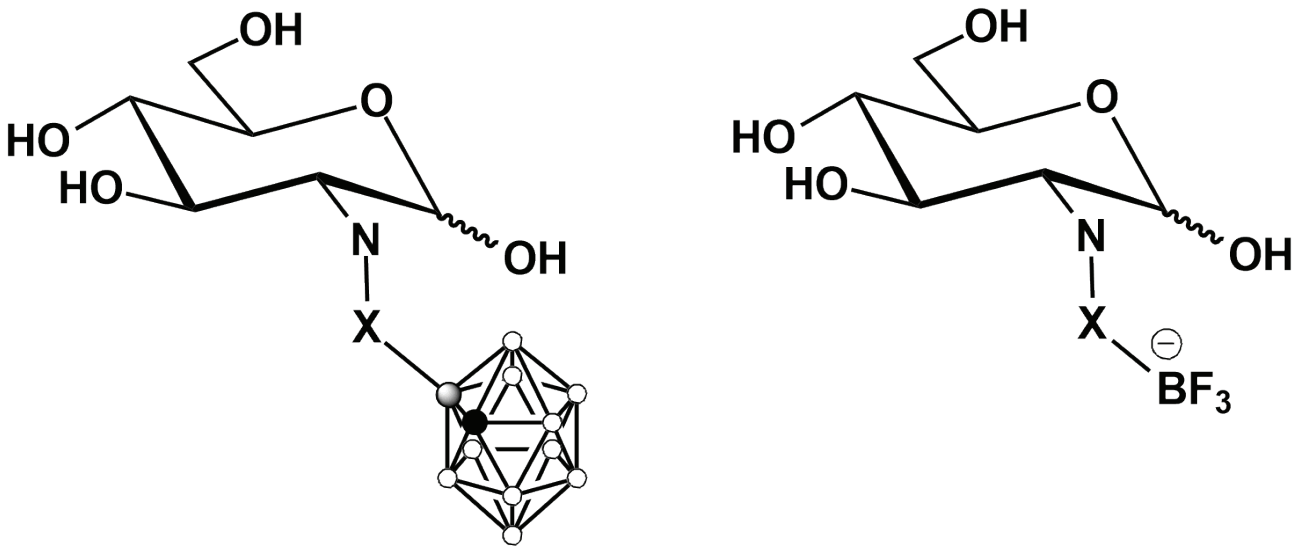

Figure captions: Fig. 1: General structure of the synthesized compounds

Boron neutron capture therapy (BNCT) is a binary radiotherapy, based on the selective accumulation of boron carriers in tumour tissues which can give excellent control over malignant tumours not responding to conventional therapies. The BNCT efficacy is based on the fission reactions that occur when the boron delivery agent captures a thermal neutron coming from a neutron flux generated by a proper external source. 4-Boronophenylalanine (BPA) is the commonly used boron delivery agent in the clinical setting as BPA is approved for clinical use; however, its performance is often not optimal. Moreover, the worldwide installation and initial use of some accelerators for research or patient treatment is increasing the interest in new and more efficient boron carriers for BNCT.
Different approaches can be followed for the development of new boron delivery agents, from small molecules to various kinds of nanocarriers.
Given that targeted therapy is a key area of focus in current biomedical research, it is relevant to ensure the continued advancement of the BNCT approach by developing new boron-containing compounds that can function as theranostic agents. These compounds should be capable of delivering the boron atom required for therapy while enabling real-time tracking of the molecule's distribution in the body.
Among different boron delivery agents, sugars derivatives can exploit the preferential uptake of sugars by tumour cells (Warburg effect). As model sugar d-glucosamine was chosen as it is transported by glucose transport proteins (GLUT) and the presence of the amino group can facilitate the derivatization of the compound. Two derivatives were synthesized, with different boron loading and physico-chemical properties. One of them was also planned to be used as a theranostic agent being easily converted into an 18-F radiolabelled derivative for positron emission tomography (PET) imaging.
The synthesis of the two model compounds, as well as preliminary toxicity data, in vitro cell uptake, and metabolic stability studies, will be provided.

Keywords: boronated sugars, theranostic, cell uptake

Poly(vinyl alcohol) potentiating the inert enantiomer of L-4-boronophenylalanine.

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L-4-Boronophenylalanine (L-BPA) can accumulate within tumors by targeting the tumor-associated amino acid transporter, LAT1. L-BPA has been the most powerful boron carrier in clinical BNCT since the first clinical demonstration of drastic therapeutic efficacy to melanoma in 1987. In 2020, we reported that L-BPA could form complexes with poly(vinyl alcohol) (PVA) via boronate esters and that the PVA-L-BPA complexes altered the internalization pathway from antiport mechanism of L-BPA through LAT1 to the LAT1-mediated endocytosis, thereby improving intratumoral retention of L-BPA and significantly augmenting BNCT effects on murine subcutaneous tumor models [1]. Meanwhile, it is well known that L-BPA is also recognized by other normal amino acid transporters, including LAT2 and $ATB^{0,+}$. Suppressing the recognition by these transporters may lead to high tumor-selective accumulation of boronophenylalanine-based drugs and increase the ratio of boron concentration in the tumor to that of normal tissues, which is expected to extend the application of BNCT. Here, we report that the seemingly inferior enantiomer of L-BPA, D-4-boronophenylalanine (D-BPA), could offer such functions in the combination with PVA. The high LAT1 selectivity of D-BPA was not well known, because previous studies reported that D-BPA did not accumulate efficiently in tumors probably due to the lower LAT1 affinity and D-BPA has not been highlighted as a clinical boron agent. However, the complex formation of D-BPA with PVA resulted in the tumor-superselective and efficient accumulation. The PVA-D-BPA complexes significantly avoided unfavorable accumulation to normal tissues, and PVA-D-BPA also exhibited extremely prolonged intratumoral retention owing to spatially controlled metabolism. That is, PVA-D-BPA was efficiently taken up by cancer cells expressing LAT1 by the LAT1- mediated endocytosis, while acidic environment in the endo-/lysosome dissociated the boronate esters and reverted the low affinity of D-BPA to LAT1, preventing the untoward efflux. PVA-D-BPA thereby accomplished complete cure of some subcutaneous CT26 tumors in mice by a single treatment.

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Keywords: boronophenylalanine, poly(vinyl alcohol), drug delivery

Various methods of synthesis and determination of the potential for use of boron carbide in BNCT therapy

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Boron carbide (B_4C) has been widely utilized in various applications, including polishing as an abrasive, ball mills as neutron absorbers, and neutron shields. Additionally, it has more recent applications in the medical field, specifically in boron neutron capture therapy (BNCT). BNCT involves the introduction of boron compounds into tumor cells or tissues and subsequent irradiation with low-energy epithermal neutrons. This results in the breakdown of the stable isotope of boron-10, which produces high-energy alpha particles and recoils the lithium-7 nuclei.
This study aimed to investigate the interaction between boron-rich boron carbide nanoparticles and selected tumor and immune phagocytic cells. The feasibility of using boron carbide nanoparticles as boron carriers in boron neutron capture therapy was explored through experiments. Boron carbide nanopowders were synthesized using two methods: carbothermic synthesis of boron carbide powders from saccharide precursors [1], and direct synthesis from elements [2]. The surface of the boron carbide and the functional groups present on it were altered to functionalize the obtained boron carbide powders. Biological tests were performed on the obtained boron carriers to determine their cytotoxicity and their influence on cell viability. The metabolic activity of the cells was assessed based on the nitric oxide release level and total amount of protein [3]. During the course of this research, the potential interaction of boron carbide nanoparticles with the tumor environment in the context of boron neutron therapy was also examined. Additionally, attempts were made to functionalize the obtained particles with the use of "cell carriers". The functionalization of the $B_{13}C_2$ nanoparticles' surface involved the attachment of sugars and their derivatives, as well as amino acids. The incorporation of amino acids during the process proved to be highly effective in the surface functionalization of the obtained nanoparticles. The presence of both a carboxyl group (-COOH) and an amino group ($-NH_2$) on the boron carbide surface significantly increased the potential for using functionalized nanoparticles. This feature enables the attachment of specific proteins to the surface of nanoparticles and the creation of targeted therapies for specific types of cancer. The materials were thoroughly characterized and monitored at each stage using spectroscopic and diffraction methods.

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Keywords: Boron Carbide (B4C), BNCT, Functionalization

An [18F]trifluoroborate-derived BPA ([18F]BBPA) for preclinical boron neutron capture therapy

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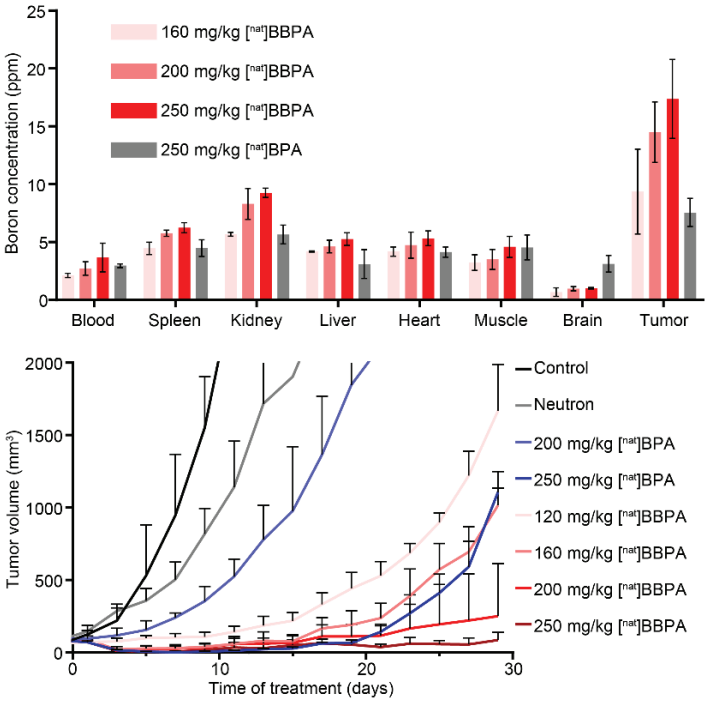

Figure captions: Organ boron concentrations(upper) and Tumor growth curve(lower) post-BNCT in B16-F10 tumor-bearing mice following tail vein injection with different doses of BBPA and BPA

Boron amino acids (BAAs), a pioneering class of amino acid biomimics, uniquely replace the traditional carboxyl group (-COOH) with a trifluoroborate group (-BF_3), enabling the achievement of ^{18}F-labeled positron emission tomography (PET) and boron neutron capture therapy (BNCT) while maintaining an identical chemical structure. This is achieved through a uniform chemical structure, with the sole variation being the substitution of ^{18}F for PET and ^{19}F for BNCT applications. In previous research, trifluoroborate-derived boronophenylalanine (BBPA), a derivative of boronophenylalanine (BPA), has been developed and proven effective on [^{18}F]BBPA-PET. It was demonstrated that [^{18}F]BBPA is transported via the large neutral amino acid transporter type-1 (LAT-1), akin to BPA. This suggests that [^{18}F]BBPA could potentially replicate the biodistribution characteristics of BPA, a well-established compound in BNCT. Clinical studies have highlighted the efficacy of [^{18}F]BBPA-PET, particularly its superior tumor uptake and remarkable tumor-to-normal brain ratio (T/N ratio, 18.7 ± 5.5, n = 11), exceeding that of common amino acid PET tracers. This has led to clinical trials utilizing [^{18}F]BBPA to achieve heightened tumor-specific accumulation for PET, offering a potential technique for brain tumor diagnosis and potentially aiding in the BNCT of brain tumors. Notably, [^{18}F]BBPA has garnered FDA and CFDA approval for clinical trials in China and the United States. The current study expands on this innovation through the comprehensive synthesis and development of BBPA for its application in PET-guided BNCT and BNCT. A key feature of BBPA is its enhanced boron delivery efficiency, due to the presence of two boron atoms in its molecular structure. This attribute was clearly demonstrated in preclinical imaging studies, which showed high tumor uptake, indicating a significant boron concentration in tumor tissue with a relatively low drug dose for BNCT. Experiments that involved the intravenous injection of varying doses of BBPA or BPA into B16-F10 tumor-bearing mice revealed that BBPA delivered higher tissue boron concentration, and 17.4 ±3.4 ppm was obtained in the tumor with 250 mg/kg BBPA but only 7.6 ± 1.2 ppm with 250 mg/kg BPA. Further, BBPA was compared with BPA for BNCT treatment response in B16-F10 tumor-bearing mice. The results showed that BBPA-based BNCT exhibited excellent therapeutic effects. Notably, similar tumor growth restraint was observed with lower doses of BBPA compared to BPA, aligning with the boron concentration results. Specifically, a dose of 250 mg/kg [^{nat}B]BBPA-BNCT almost completely inhibited tumor growth over a 29-day research period, underlining the successful tumor management achievable with BBPA-BNCT. The higher boron delivery efficiency of BBPA suggests a reduced dose requirement in clinical applications, and it is anticipated that even better efficacy could be achieved with ^{10}B-enriched BBPA ([^{10}B]BBPA) as opposed to natural boron ([^{nat}B]BBPA) in BBPA-BNCT. In conclusion, this study not only marks a significant stride in the synthesis and development of a novel BAA but also underlines its potential as a dual-function theranostic agent for both PET imaging and BNCT. The dual functionality of BBPA, combined with its effective targeting and retention in tumor tissues, firmly establishes it as a promising candidate in the realm of oncological theranostics. The outcomes of this research are poised to make a substantial impact on precision medicine in cancer therapy, offering new avenues for enhanced patient care and outcomes.

Keywords: Trifluoroborate boronophenylalanine; PET; BNCT; Theranostics

Gadolinium-Boron Conjugated Albumin: Pioneering MRI-Guided Neutron Capture Therapy

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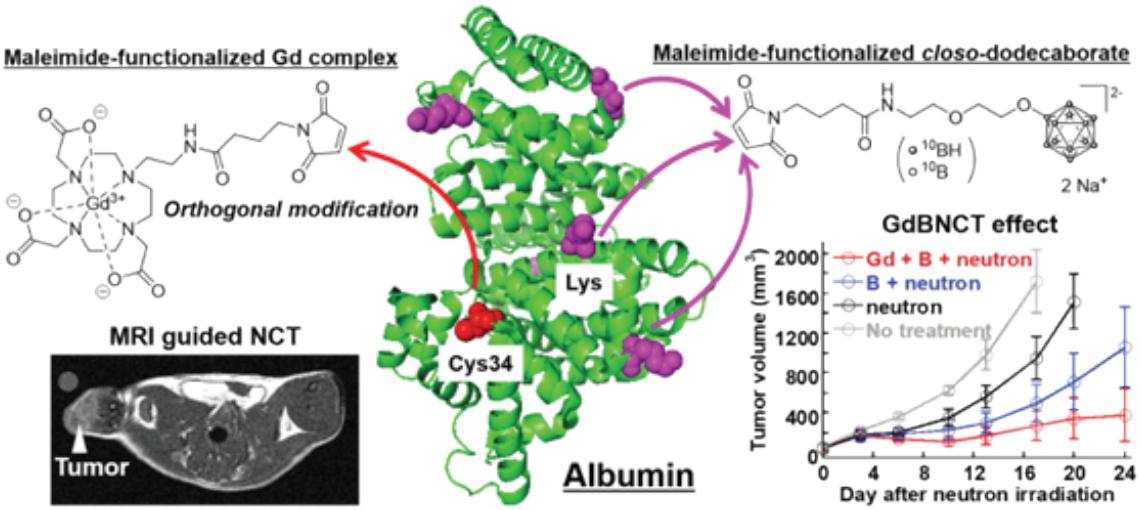

Figure captions: Figure 1. MRI-Guided Neutron Capture Therapy

While sodium mercaptoundecahydro-closo-dodecaborate (BSH), a boron cluster containing twelve boron atoms, was initially used for the treatment of glioblastoma, L-boronophenylalanine (BPA) is currently the most-used boron agent in clinical BNCT. This is because it is selectively taken up by tumors through L-type amino acid transporter 1 (LAT1), which is overexpressed in various cancer cells. Furthermore, ^{18}F-labelled BPA-based positron emission tomography (PET) is available to estimate pharmacokinetics of BPA, enabling the prediction of the appropriate timing of neutron irradiation after administration of BPA. However, it remains challenging to apply BNCT for tumors which express low levels of LAT1. To broaden cancer indications of BNCT, boron agents with different delivery mechanisms from BPA have been developed. Previously we developed a maleimide-functionalized closo-dodecaborate (MID) that binds to bovine serum albumin (BSA) as a boron carrier.[1] The MID-BSA conjugate efficiently accumulated in tumors of mouse models due to enhanced permeability and retention (EPR) effect. In order to achieve the highest BNCT effect, the thermal neutron should be irradiated at the timing when the boron concentration in tumors reaches the maximum. Therefore, non-invasive monitoring of boron agent biodistribution is required in advance of neutron capture therapy. Magnetic resonance imaging (MRI) could be a powerful approach for this purpose and gadolinium (Gd) contrast agents with boron sources have been developed for MRI-guided BNCT.[2-4] One of the stable isotope ^{157}Gd (natural abundance = 15.7%) also captures thermal neutron, the cross section of which is 66 times larger than ^{10}B. The neutron capture reaction of ^{157}Gd produces ^{158}Gd and 7.94 MeV of total energy. The large fraction of energy is released as γ-ray which can damage cells 100 μm far away while the rest energy mainly results in internal conversion electrons and Auger electrons, capable of destructing DNA inside of cells. Gadolinium is therefore a potential agent for gadolinium neutron capture therapy (GdNCT) that has additive effects to enhance BNCT under MRI guide. In this study, we developed a gadolinium-boron conjugated albumin (Gd-MID-BSA) for MRI-guided neutron capture therapy (Fig. 1). Gd-MID-BSA was prepared by labelling bovine serum albumin with a maleimide-functionalized gadolinium complex and a maleimide-functionalized closo-dodecaborate orthogonally. The accumulation of Gd-MID-BSA in tumors in CT26 tumor-bearing mice reached the maximum at 24 h after the injection, as confirmed by T_1-based MRI and biodistribution analysis using inductively coupled plasma optical emission spectrometry. The concentrations of boron and gadolinium in the tumors exceeded the thresholds required for BNCT and GdNCT, respectively. The boron concentration ratios of tumor-to-blood and tumor-to-normal tissue satisfied the clinical criteria, indicating the reduction of undesired nuclear reactions of endogenous nuclei. The molar ratio of boron to gadolinium in the tumor was close to that of Gd-MID-BSA, demonstrating the accumulation of Gd-MID-BSA in the tumor can be evaluated by MRI. Thermal neutron irradiation with Gd-MID-BSA resulted in significant suppression of tumor growth compared to the group injected with a boron conjugated albumin without gadolinium (MID-BSA). The neutron irradiation with Gd-MID-BSA did not cause apparent side effects. These results demonstrate that the conjugation of gadolinium and boron within the albumin molecule offers a novel strategy for enhancing the therapeutic effect of BNCT and the potential of MRI-guided neutron capture therapy as a promising treatment for malignant tumors.[5]

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Keywords: albumin, MRI, gadolinium, boron, NCT

Innovation of Boron Delivery: Albumin-Based Molecularly Targeted BNCT

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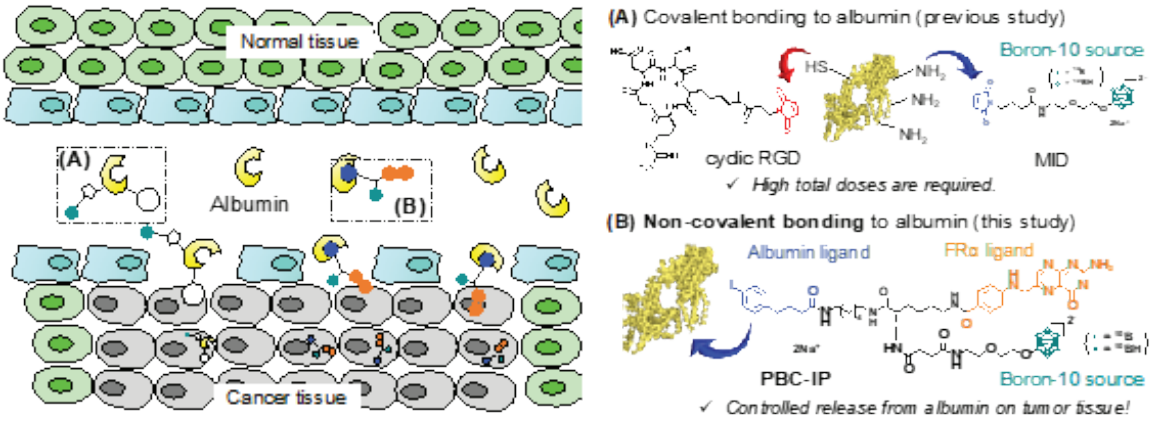

Figure captions: Fig. 1. Albumin-based boron delivery system for BNCT.

Boron neutron capture therapy (BNCT) has been applied for clinical trials on glioblastoma (GBM) patients since 1950s. While L-4-boronophenylalanine (BPA) has been approved for unresectable, locally advanced, or locally recurrent head and neck cancers in Japan,[1] the development of new boron agents is still demanded for treating GBM patients. Two essential criteria for the development of boron agents for BNCT include (1) selective accumulation in tumor cells and (2) selective delivery to tumor tissue.
Serum albumin, a key drug-delivery protein, is known to accumulate in tumor tissues through the enhanced permeability and retention (EPR) effect. We have developed maleimide-functionalized closo-dodecaborate (MID), a small boron agent that selectively accumulates in tumors by covalently conjugating with albumin, demonstrating efficient BNCT effects in mice with subcutaneous tumors [2] and rats with orthotopic brain tumors.[3] Furthermore, we developed cyclic RGD (cRGD) peptide-conjugated MID-albumin, produced through orthogonal modification targeting αvβ3 integrins that overexpress in many cancer cells (Fig. 1A).[4,5]
However, high total doses are still required to achieve therapeutic levels of intratumoral boron concentrations. To overcome this issue, we developed a novel boron agent, PBC-IP, which consists of three functional groups: FRα-targeting, ^{10}B resource (twelve ^{10}B atoms in the molecule), and albumin-binding moieties (Fig. 1B). PBC-IP has remarkably low cytotoxicity and is water soluble, allowing it to be administered without any solubilizers. We examined cell uptake of PBC-IP in these four cell lines. BPA was used as a control. Surprisingly, the accumulation of PBC-IP was 10 to 20-fold higher than that of BPA in the glioma cell lines, C6, F98 and U87MG, whereas that of both PBC-IP and BPA were similar in A549 cells. PBC-IP also exhibited superior intratumor accumulation compared to BPA by i.v. administration, resulting in efficient tumor growth suppression after thermal neutron irradiation. Administrated via convection-enhanced delivery (CED), PBC-IP selectively accumulated in glioma orthotopic rat models, achieving remarkable BNCT effects. Survival rates at 180 days post-BNCT were 50% in the PBC-IP group and 70% in the combined BPA and PBC-IP groups, with no residual brain tumors.[6] This presentation outlines our strategy for an albumin-based boron delivery system.

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Keywords: albumin, integrin, folate receptor, glioma

Boron measurements by Argon Plasma Inductively Coupled an Optical Emission Spectrometer (ICP-OES) in Boron Neutron Capture Therapy (BNCT) in Argentina.

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BNCT is a binary therapy that has been used primarily to treat different types of cancer, because it can selectively target neoplastic tissue. The success of this therapy depends on the ability of the boron compound used to selectively concentrate on the tumor and the total physical dose absorbed by the tumor cells. In this context, boron quantification is essential to calculate the therapeutic dose in BNCT. Analytical chemistry procedures are involved in the quantification of different boron compounds. Although there are different techniques for measuring boron, ICP-OES has proper characteristics in terms of limit of detection, precision and accuracy. This technique avoids additional exposure to radiation, unlike other techniques used such as Positron Emission Tomography, strengthening the safety of patients and workers at time of the irradiation.
ICP-OES has been adopted as a routine technique by most of the international BNCT centers for the quantitative determination of total boron. Through this technique, it is possible to quantify different boron compounds in samples from clinical and research protocols. There are different analytical methods that can be applied to various organic and inorganic matrices. In addition, this method combines important features such as the possibility of high sample throughput, very low detection limits, and practical prerequisites for sample preparation. In Argentina, the BNCT project has 2 ICP-OES devices: the PERKIN-ELMER brand, located at the Bariloche Atomic Center, for whole blood measurements in clinical and preclinical treatments, and the AGILENT brand, located at the Constituyentes Atomic Center for cell and tissue measurements, among others. Introducing samples for these methods usually requires liquid samples, which after passing through a nebulizer are finally injected as aerosols. Samples that are not liquid must first undergo digestion or a comparable process of dissolution. Whole blood samples are introduced into the plasma with the addition of a surfactant. Cells and tissues are digested with different acids.
Considering the importance of determining boron concentration, this work describes the advantages and disadvantages of the ICP-OES method compared to others methods to measure boron and the methodology based on current protocols that study the absorption of this element from the different boron-releasing compounds: BPA, nanoparticles, antibodies and boron clusters combined with tyrosine kinase inhibitors.

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Keywords: ICP-OES, BORON COMPOUNDS, ANALYTICAL CHEMISTRY

AI-based optimization of physicochemical properties of polymer-drug conjugates for BNCT

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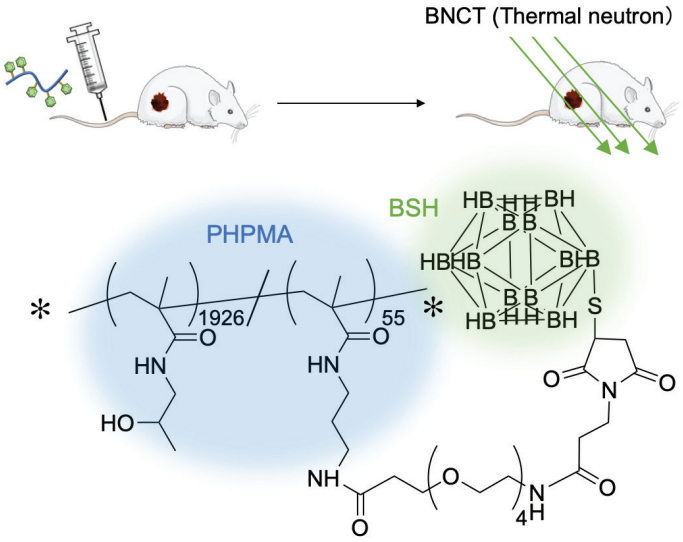

Figure captions: Chemical structure of PHPMA-BSH

4-Boronophenylalanine (BPA) is taken up via LAT1, which is highly expressed on many kinds of cancer cells, permitting tumor-selective accumulation and significant therapeutic effects. Meanwhile, the development of boron drugs for LAT1-negative cancers has been still limited. In order to expand the BNCT-applicable disease, it is important to develop new boron drugs with different mechanisms of tumor accumulation from that of BPA. Generally, in designing drugs for BNCT, the boron concentration in the tumor should be >25 ppm for the efficient therapeutic effect and the boron concentration ratio of the tumor to the blood (T/B ratio) or the tumor to the surrounding normal organ (T/N ratio) should be >2.5 to avoid undesirable radiation damage to the normal tissue. Furthermore, from the viewpoint of practical use, the drugs should be easy to synthesize and should not cause untoward effects. In this regard, poly(N-(2-hydroxypropyl)methacrylamide) (PHPMA) may be a promising platform to construct such drugs. Owing to the high water solubility and biocompatibility, PHPMA has been utilized as plasma expanders and hydrogels [1]. In addition, large quantities of PHPMA can be easily synthesized, and molecular weight distribution, which is a critical parameter determining biodistribution, can be fine-tuned by reversible addition-fragmentation chain transfer (RAFT) polymerization [2]. Herein, we developed PHPMA-based drug delivery systems for BNCT. First, we synthesized PHPMA with various molecular weights (M_n: 50,000, 130,000, and 330,000) by RAFT polymerization, using V50 as the initiator and 4-cyanopentanoic acid dithiobenzoate as the RAFT agent. Cy5 was then introduced to the polymers, and their biodistribution was examined in subcutaneous CT26 tumor mouse models. The PHPMA with M_n of 50,000 was immediately excreted from the kidneys and showed low tumor accumulation. Meanwhile, increasing the molecular weight led to reduced renal excretion, resulting in higher blood circulation and higher tumor accumulation. We also evaluated the design of drug delivery systems in in silico using quantitative structure-activity relationship (QSAR) and physiologically-based pharmacokinetic (PBPK) models with an AI-based nano-tumor database [3]. The result estimated that the highest tumor accumulation can be achieved by the physicochemical properties with the size about 100 nm with the charge neutral, which appeared to be similar to the characteristics of the PHPMA with M_n of 330,000. We therefore conjugated BSH with PHPMA at the M_n of 330,000 and evaluated the pharmacokinetics and antitumor effects. The BSH-conjugated PHPMA showed a significant improvement in tumor accumulation and therapeutic effects compared to BSH. PHPMA should be a promising platform to construct drug delivery systems for BNCT.

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Keywords: Drug delivery, Polymer, Artificial intelligence

Boron encapsulated in a liposome or a lipid nanoparticle can be used for combinational neutron capture therapy

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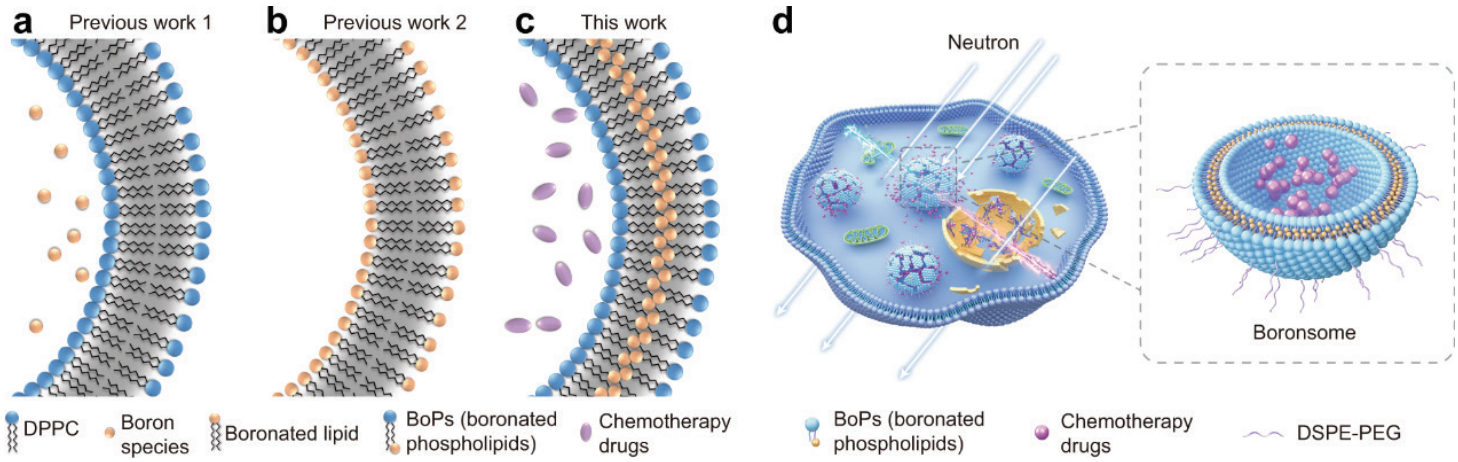

Figure captions: Schematic illustration of boronated liposomes for BNCT.

Boron neutron capture therapy (BNCT) is a binary, biochemically targeted radiotherapy, which provides excellent tumour control over inoperable malignant tumours. The therapeutic effect of BNCT is based on the capture reactions that occur when tumour-targeted boron delivery agents are irradiated with thermal neutrons. Therefore, the high-selective delivery of sufficient boron into tumour cells is the key to developing BNCT drugs, yet is still an unmet need.
Boronated tyrosine derivative 4-boronophenylalanine (BPA) is the most widely used boron delivery agent in the clinical setting. However, deficient uptake has been a long-standing problem since the first application of BPA in 1987 as well as other small-molecule based boron delivery agents. To overcome this problem, boron-enriched nanocarriers have been intensively studied as alternative candidates for boron delivery agents during the last two decades. Among them, liposomes are considered to be one of the most efficient and clinical-relevant delivery vehicles, yet several drawbacks have hampered liposomes to become practical boron carriers in clinics: (1) liposome structures currently reported are mainly based on boron-enriched small molecules encapsulation strategy, of which the loading capacity is limited and may have cargo leakage to off-tumour tissues; (2) application of unusual boranes which are short of in vivo stability could induce un-expected biochemical toxicity and immunogenicity; (3) absence of suitable properties to allow their detection by noninvasive imaging techniques to explore in vivo biodistribution of boron agents to ensure the accuracy of neutron irradiation and to improve efficacy.
Here, we report boronsome, a carboranyl-phosphatidylcholine based liposome for combinational BNCT and chemotherapy. Theoretical simulations and experimental approaches illustrate high stability of boronsome. Then positron emission tomography (PET) imaging with Cu-64 labelled boronsome reveals high-specific tumour accumulation and long retention with a clear irradiation background. In particular, we show the suppression of tumour growth treated with boronsome with neutron irradiation and therapeutic outcomes are further improved by encapsulation of chemotherapy drugs, especially with PARP1 inhibitors. In sum, boronsome may be an efficient agent for concurrent chemoradiotherapy with theragnostic properties against malignancies.

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Keywords: Boronsome; BCNT; PET; lipid nanoparticles

Artificial Intelligence Assessments of the Small Molecular Boron Agents for Boron Neutron Capture Therapy

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Boron neutron capture therapy (BNCT) is a highly targeted, selective and effective technique to cure various types of cancers, with less harm to the healthy cells. In principle, BNCT treatment needs to distribute the boron-10 (10B) atoms inside the tumor tissues, selectively and homogeneously, as well as to initiate a nuclear fission reaction by capturing sufficient neutrons which releases high linear energy particles to kill the tumor cells. In BNCT, it is crucial to have high quality boron agents with acceptable bio-selectivity, homogeneous distribution and deliver in required quantity, similar to chemotherapy and other radiotherapy for tumor treatment. Nevertheless, boron drugs currently used in clinical trials yet to meet the full requirements. On the other hand, BNCT processing has opened up the era of renaissance due to the advanced development of the high-quality neutron source and the global construction of new BNCT centers. Consequently, there is an urgent need to use boron agents that have increased biocapacity. Artificial intelligence (AI) tools such as molecular docking and molecular dynamic simulation technologies have been utilized to develop new medicines. To speed up the screening process for small molecules of boron agents, we employ AI technologies here. The boron agent and interacting protein's binding energy (BE), geometric shape complementary score (GSCS) and dynamic simulation results will certainly be helpful to researchers in optimizing druggable boron agents for the BNCT application. This work reports the in silico docking and molecular simulation results of the optimized small boron agents, such as 4-borono-L-phenylalanine (BPA) and fluoroboronotyrosine (FBY) with optimized proteins like the L-type amino acid transporter 1 (LTA1, also known as SLC7A5), epidermal growth factor receptor (EGFR) and cellular myelocytomatosis (MYC), will be examined. The clinical status of these proteins (SLC7A5, EGFR, and MYC), which are highly relevant to cancers that may be treated with BNCT, has been assessed using bioinformatics technology and discussed accordingly.

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Keywords: BNCT, AI, boron agent, RMSD

Sensitive sites of subcellular organelles of U251 glioma cells in boron neutron capture therapy using L-4-Boronophenylalanine

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Background: In radiotherapy, the identification of radiation-sensitive subcellular organelles in tumor cells is pivotal for enhancing treatment efficacy. Boron Neutron Capture Therapy (BNCT) stands out due to its selectivity, radiobiological effectiveness, brevity, and minimal side effects. Unlike conventional radiotherapies, BNCT leverages α particles and lithium ions for therapeutic impact. While the nucleus and membrane are known to be sensitive in traditional radiotherapies like X-ray and electron beam, the specific organelle sensitivity in BNCT is less explored.
Materials and Methods: U251 glioma cells underwent BNCT using the accelerator-based system NeuPex Block-I by Neuboron Therapy System Ltd., Xiamen, China. Post 30-minute incubation with ^{10}B-enriched L-4-Boronophenylalanine (BPA, Neuboron Bio-SciTech Co., Ltd.) at 54 ppm, cells were exposed to 8 minutes of neutron irradiation. Subcellular organelle sensitivity—encompassing the cell membrane, endoplasmic reticulum, mitochondria, and nucleus—was assessed via trypan blue staining, LC3 and Beclin-1 protein expression(LC3 and Beclin-1 are two important proteins in the process of autophagy, with LC3 being responsible for the formation of autophagosomes during autophagy), CCK-8(the principle of CCK-8 relies on the reduction of WST-8 to a yellow formazan product by mitochondrial dehydrogenases), and colony formation assays.
Results: Trypan blue exclusion in U251 cells post-BNCT (93.30%, 94.70%, 88.30% at 24, 78, 96 hours, respectively) indicates minimal cell membrane damage. No significant changes in LC3II/LC3I ratios or Beclin-1 expression suggest that BNCT mediated by BPA does not induce autophagy in this cell line, thereby inferring negligible impact on the endoplasmic reticulum. CCK-8 assays, reflecting mitochondrial dehydrogenase activity, showed slight sensitivity (survival rates of 102%, 77%, 72% at 24, 78, 96 hours). However, a significant reduction in proliferative capacity (10% survival in colony formation assays) highlights the nucleus as the most sensitive organelle to BNCT mediated by BPA.
Conclusion: These observations suggest a hierarchical sensitivity of U251 cell organelles to BNCT, ranked as: nucleus > mitochondria > endoplasmic reticulum > cell membrane.

Keywords: BNCT; Radiation Damage; Subcellular Organelle;

New boronophenylalanine (BPA) derivatives for the treatment of head and neck cancer: biodistribution, microdistribution and BNCT studies in the hamster cheek pouch oral cancer model

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BPA (boronphenylalanine) has been demonstrated as an effective boron carrying agent for BNCT in multiple pathologies and is approved in Japan for the treatment of recurrent head and neck cancer. Our group, originally lead by Amanda Schwint, has previously demonstrated the therapeutic effect of BNCT mediated by BPA in the hamster cheek pouch oral cancer model, a widely accepted model to study oral cancer development, therapies and induced toxicity. The oral cancer induced in this model is surrounded by precancerous tissue, this is advantageous as it allows for the study of radiotoxicity by monitoring for mucositis. Although BPA meets several of the requirements of an ideal boron compound for BNCT, notably significant tumor control, it also has limitations. These include solubility, capacity to carry boron atoms and BNCT mediated severe mucositis which can be defined as a dose limiting toxicity. New boron compounds that could overcome these limitations and improve therapeutic effect are of interest. With this in mind, we evaluated the biodistribution, microdistribution and BNCT therapeutic effect of two BPA derivatives, TC440 and TC441 developed by TAE Life Sciences Drug Development Division. Oral cancers were induced in 6-8 weeks old Syrian hamsters using the carcinogen dimethylbenzantracene (DMBA) applied orally twice a week for 12 weeks. Tumor bearing animals were used for biodistribution/microdistribution studies employing: TC440 (i.v.) 40.2 mg B/kg (800 mg TC440/kg) (n= 3); TC441 (i.v.) 40.2 mg B/kg (800 mg TC441/kg) (n= 3); BPA (i.v.) 40.2 mg B/ kg (778 mg BPA/kg) (n= 3); BPA (i.v.) 15.5 mg B/kg (300 mg BPA/kg) (n= 3). In vivo BNCT studies at 2.6 Gy absorbed dose to precancerous tissue were performed at the RA-3 nuclear reactor in Buenos Aires, Argentina. Boron concentration values for tumor, precancerous tissue, normal pouch and blood were measured by ICP-OES. The therapeutic effect on tumors and mucositis in precancerous tissue was assessed for up to 28 days after BNCT. Gross boron concentration values in the tumor for TC440, TC441 and BPA at the 40.2 mg B/kg dose were similar and significantly higher than BPA at the 15.5 mg B/kg dose (65±15 vs 61±7 vs 55±28 vs 28±7ppm respectively, $p<0.01$). Precancerous and normal tissue boron concentration were in the range of 32-36 ppm for all 40.2 mg B/kg doses, which is significantly higher than BPA dosed at 15.5 mg B/kg (12-14 ppm, $p<0.01$). For all 40.2 mg B/kg doses, the tumor/precancerous tissue ratio was approximately 2:1. However, the values recorded in the precancerous tissue surrounding tumors were high enough to potentially cause severe radiotoxic effects. Consequently, a high percentage of animals with severe mucositis were observed in all groups. BNCT in vivo studies showed that overall tumor response (ORR) after TC440/BNCT at 2.6 Gy was slightly higher than BPA/BNCT at 40.2 and 15.5 mg B/kg (73% ORR v 67-68% ORR respectively). In contrast, despite the minor differences in ORR, the percentage of tumors with complete remission (complete response, CR) was higher in the TC440/BNCT group versus the BPA/BNCT group dosed at both 40.2mg/kg and 15.5 mg B/kg (48% vs 29% and 23% respectively). Moreover, some of the tumors where a CR was observed were larger tumors and these have been seen to be refractory to BNCT in past studies. Ongoing BNCT studies, using TC441 at 2.0 Gy absorbed dose, will evaluate if lowering the dose will induce less severe mucositis without affecting tumor control. Autoradiography, studies employing TC440, TC441 and BPA (40.2 mg B/kg dose) versus previously reported results for BPA (15.5 mg B/kg), are under evaluation to explain the differences in tumor response between protocols. Data from these studies will be reported at the conference.

Keywords: BNCT, BPA, oral-cancer, novel-drugs, complete-response

IN VITRO STUDIES OF RADIOSENSITIVITY TO THE BORON NEUTRON CAPTURE THERAPY (BNCT) IN THE UNDIFFERENTIATED THYROID CANCER (UTC)

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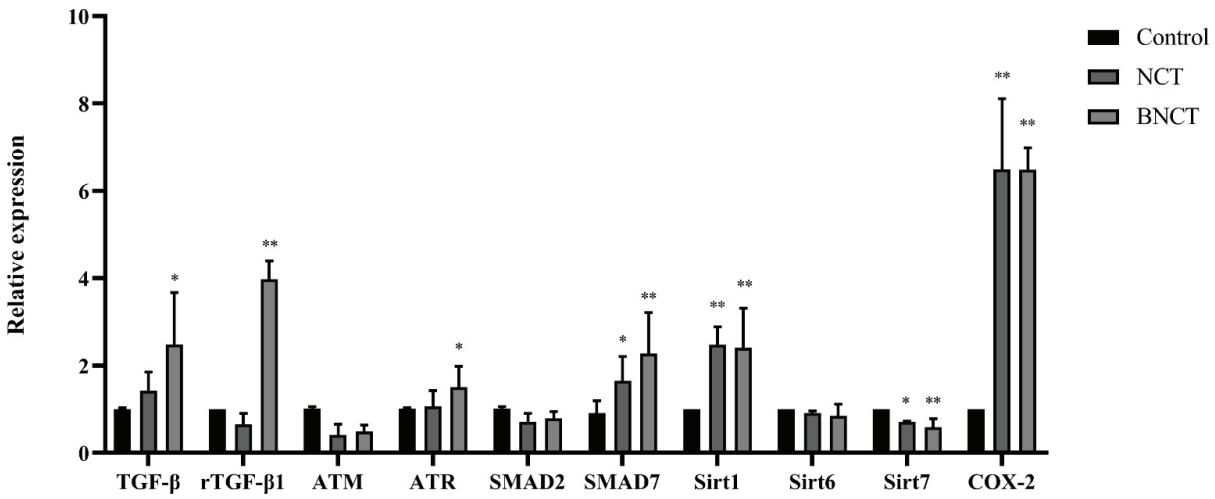

Figure 1: mRNA expression of ATM, ATR, TGFbeta, rTGF beta, Smad 2, Smad 7, Sirt 1, 6 and 7 and COX 2 in cells of undifferentiated thyroid carcinoma (8505C) non irradiated (Control), irradiated with neutrons alone (NCT) or with neutrons plus BPA (BNCT). NCT and BNCT vs Control *p<0.05 and **p<0.01

The undifferentiated thyroid carcinoma (UTC) is a highly invasive and rapidly growing malignant tumor that currently lacks effective treatment (1). We have already demonstrated in several preclinical studies that boron neutron capture therapy (BNCT) is a promising therapy to UTC (2). However, as happen with chemo or conventional radiotherapy, tumor resistance has been shown to lead to the recurrence of the illness. It is known that the radiation field produced in the tumor during the application of BNCT consists of a mixture of radiation of different quality that produces DNA damage and triggers different processes such as: arrest in the cell cycle, cell death or DNA repair. Previously in a thyroid carcinoma cell line we have described and quantified the complexity of the damage produced and we have shown that the main activated repair pathway is homologous recombination (HR) (3). Currently it is known that there are other proteins that are activated during the irradiation and regulate the DNA repair, such as nuclear sirtuins (Sirt 1, 6 and 7) which are NAD-dependent deacetylases or the TGFbeta/Smad via (4,5). Some other proteins like COX 2, are released into the tumor microenvironment and promote apoptotic resistance, proliferation, inflammation, invasion, and metastasis of cancer cells (6). In the present studies, with the objective of increasing the radiosensitivity of the UTC to BNCT, we explored the expression of different proteins that belong to cellular pathways independent and secondary to the classic repair pathways (NHEJ and HR) and that are activated to maintain genomic stability after ionizing radiation. In these experiments, cells from the human UTC cell line (8505C) were seeded in 25 cm ^{2}plates (T25) and divided into the following 3 groups: Control (without boron and non-irradiated); NCT (neutron beam alone); BNCT (borophenylalanine + neutrons). The 0.14M borophenylalanine (^{10}BPA) solution was added at a concentration of 10 ppm boron-10 and incubated for 2 hours. Then the cells were irradiated in the nuclear reactor RA3 (Ezeiza Atomic Center) (neutron flux=1.10^{10} n/cm^2 sec^{-1}) for the time calculated to obtain a total absorbed physical dose of 3Gy. Post irradiation and after 2 hours of incubation at 37°C, RNA extraction with Trizol and real-time PCR with specific primers pairs for each gene (TGFbeta, rTGFbeta, Smad 2, Smad 7, ATR, ATM, Sirt 1, Sirt 6, Sirt 7 and COX 2) were performed. The expression of the COX 2 protein

was analyzed at 24 h post treatments by immunohistochemistry. The results showed in both irradiated groups compared to the Control group, a significant increase of the expression of the following genes: ATR, TGFbeta, rTGFbeta, Smad 7, Sirt 1 and COX 2 ($p<0.01$). The protein expression of COX 2 increased significantly in both irradiated groups with respect to the Control group. These studies allow us to evaluate possibility of radiosensitizing increasing the effectiveness of BNCT for thyroid cancer using inhibitors of the proteins involved in genomic homeostasis that were found to be overexpressed.

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Keywords: undifferentiated thyroid carcinoma, genomic stability,

The Radiobiological Mechanisms of Anti-Tumor Immunity Induced by Boron Neutron Capture Therapy

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Boron neutron capture therapy (BNCT) stands out as a binary and highly-selective form of radiotherapy. This innovative approach deposits high energy specifically to boron-containing tumor cells, effectively sparing adjacent normal cells from damage. While the therapeutic benefits of BNCT over traditional radiotherapy are gaining recognition, the radiobiological mechanisms underlying BNCT remain only partially understood and warrant further in-depth investigation.
Recent studies have showed the abscopal effect of BNCT, a phenomenon we have also validated in a mouse model. This suggests the intriguing occurrence of BNCT-induced immune responses. Despite the heterogeneous distribution of boron carriers within tumors, BNCT exhibits the remarkable capability to eliminate tumors, hinting at a potential involvement of the immune system. Moreover, owing to the selectivity of BNCT, immune cells within the tumor microenvironment remain unharmed. This preservation of immune cells creates a conducive environment for immune activation. Consequently, delving into the impact of BNCT on the immune microenvironment becomes imperative, as such insights hold the promise of optimizing therapeutic efficacy.
We employed a systematic approach utilizing single-cell RNA sequencing (scRNA-seq) to investigate the comprehensive changes in tumor tissue following BNCT treatment. Single-cell RNA sequencing is a high-resolution tool for studying gene expression at the single-cell mRNA level and has found widespread use. Mice were treated with BPA-BNCT or X-ray radiation, respectively, and tumor tissues were collected for scRNA-seq analysis. The results of the single-cell sequencing studies revealed that BNCT effectively stimulated anti-tumor immunity. A subset of tumor cells treated with BNCT underwent immunogenic cell death, initiating the release of various mediators into the extracellular space as danger signals. This process recruited inflammatory cells into the tumor microenvironment, activating antigen-presenting cells. Consequently, this led to an expanded repertoire of tumor-specific CD8+ T cells and enhanced cytotoxic T-cell function. This study highlights the potential of BNCT to instigate a systematic antitumor immune response. Simultaneously, it supports the prospect that combining BNCT with immunotherapy could lead to superior therapeutic effects, potentially reducing neutron dosages.

Keywords: Radiobiology, Anti-tumor immunity, scRNA-seq

Biofunctionalized boron carbide nanoparticles as targeted boron compounds in boron neutron capture therapy

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Boron neutron capture therapy (BNCT) is based on the nuclear reaction that occurs when boron-10 is irradiated with low-energy thermal neutrons. As a result of this process, the nucleus of the boron-10 isotope is split, which releases energy that destroys cancer cells (1). One of the main challenges for the development of BNCT is the search for selective compounds that provide the required amount of boron in the tumor environment. An interesting aspect is research on nanometric structures such as inorganic nanoparticles as boron carbide or boron nitride. These nanoparticles are characterized by high boron content in their structure. Through targeted synthesis and extensive physicochemical analysis, modification of their surface allows to create the variants specifically targeted to the tumor environment (2). In our research, we modify boron carbide nanoparticles with antibodies, targeted at receptors found in cancer cells, in order to increase the selectivity of their interaction with the tumor environment.
Three cancer cell lines with different levels of expression of low-density lipoprotein receptor (LDLR) and epidermal growth factor receptor (EGFR) on the surface were selected for the study: T98G (glioblastoma multiforme), PC-3 (prostatic adenocarcinoma), SCC-25 (squamous cell carcinoma). The presence of receptors was determined both at the mRNA level using real-time PCR and surface expression using flow cytometry. Cytotoxicity tests of the obtained boron carbide nanoparticles modified on the surface with anti-LDLR and anti-EGFR antibodies were performed on selected cell lines. Then, using flow cytometry and fluorescence microscopy techniques, the interaction of functionalized boron nanoparticles with cells was analyzed.
The results of our research did not show a significant impact of boron carbide surface functionalization on the cytotoxicity of the tested compound. Selected cell lines differed in the level of LDLR and EGFR expression on their surface and the SCC-25 line showed the highest expression level for both receptors. Tests performed with a fluorescence microscope and a flow cytometer confirmed the highest level of interaction of anti-EGFR antibody-modified nanoparticles with the SCC-25 line compared to the other tested cancer cell lines. In conclusion, as a result of the functionalization of boron carbide nanoparticles, stable complexes were obtained showing affinity for cancer cells with a high level of expression of a specific receptor on their surface. This study was supported by National Science Center, Poland Grant Numbers UMO-2019/33/B/NZ5/02212

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Keywords: boron carbide, BNCT, cancer cells

The role of GM-CSF in the early response to BNCT

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BNCT (boron neutron capture therapy) has emerged as a promising approach for treating various solid cancers, including those affecting the head and neck, demonstrating significant efficacy in clinical studies. The unique advantage of BNCT lies in its ability to target and eliminate tumor cells selectively. High mobility group box 1 (HMGB1) is a proinflammatory ligand that binds to the receptor for advanced glycation end-products (RAGE) and Toll-like receptor (TLR). It is also involved in the DNA damage response and cell death. We recently observed that the extracellular release of HMGB1 was significantly enhanced in SAS cells 24 hours after BNCT, and plasma HMGB1 levels were higher in an SAS xenograft mouse model 3 days post-BPA-based BNCT compared to non-irradiation controls. HMGB1 was detected in both nuclei and cytoplasm in tumor cells. In our previous study, we found that gene expression of CSF2, which codes granulocyte-macrophage colony-stimulating factor (GM-CSF), and GM-CSF concentration in conditioned medium (CM) were increased in a time and dose-dependent manner in SAS cells at early stages after BNCT carried out with ^{10}B-boronophenylalanine (BPA). GM-CSF is known to promote dendritic cell differentiation from precursors, enhance the antigen presentation process and adaptive immune responses, and is also used in the clinical application of chemo- and radiotherapy. Pre-clinical and clinical data support the role of GM-CSF as an immune adjuvant in the treatment of malignant solid and liquid tumors, and GM-CSF has been used for tumor vaccines in combination with ipilimumab (anti-CTLA-4) or pembrolizumab (anti-PD-1). Our study also observed the increase of GM-CSF in the plasma from of mice harboring SAS cell xenografts 3 days after BNCT. To examine the significance of GM-CSF on the tumor immune environment, we added recombinant mouse GM-CSF (rmGM-CSF) to a conditioned medium of mouse melanoma B16 cells that did not express GM-CSF and investigated its effect on the differentiation of mouse bone marrow cells. B16 cells were irradiated with a therapeutic dose of BNCT, and 24 hours later, bone marrow cells were cultured in conditioned medium from B16 cells with or without rmGM-CSF for 6 days, and the differentiated adherent cells were collected. As a result, the adherent cells induced to differentiate were shown to be macrophage-like cells by flow cytometry. We investigated the type of macrophages after BNCT irradiation using the cytokine expression profile. The results of macrophage typing using real-time PCR cytokine expression profiles showed that M1 type markers such as IL6, a factor involved in antigen presentation in adherent cells, were particularly increased, while M2 type markers were decreased. These results suggested that BNCT induces pro-inflammatory and anti-tumor M1-type macrophages. Furthermore, T cells derived from mouse subiliac lymph nodes were added to those induced macrophage-like cells, and after culturing for 5 days, the proliferation of T cells was examined using fluorescent dye labeling. As a result, we found that induced macrophages promoted T cell proliferation induction in the presence of 50 ng/ml GM-CSF. These results imply that the induced macrophages from the bone marrow cells may potentially contribute to tumor immune responses locally or systemically when GM-CSF is boosted. GM-CSF derived from cancer cells after BNCT may play an important role in the inflammatory/immune cascade in the tumor environment at least as an early response.

Keywords: melanoma GM-CSF macrophages Tcells

Exploring boron neutron capture therapy as a promising treatment for spinal cord gliomas: in vivo efficacy in rat models

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Background: Boron neutron capture therapy (BNCT) is a type of targeted particle radiation therapy with potential applications at the cellular level. An accelerator neutron source has been successfully developed, and BNCT using boronophenylalanine (BPA) for head and neck cancer is now covered under insurance in Japan. Based on its results in nuclear reactors, it is expected to be a treatment for invasive cancers such as malignant glioma and high-grade meningioma. Like intracranial malignant glioma, spinal cord malignant glioma is also considered to have a poor prognosis as an invasive cancer. Since surgical removal is limited to the removal of the tumor mass from the viewpoint of neurological function, postoperative chemotherapy and radiotherapy, which can be targeted to the invasive area, are important. However, there is insufficient evidence regarding their usefulness because this is a rare disease. In the case of recurrence after radiation therapy, the next treatment option is limited in terms of tolerated dose of radiation, and there is currently no effective treatment. This study evaluated the efficacy of BNCT in a rat Spinal Cord Glioma (SCG) model employing the overall survival time and the Basso, Bresnahan, and Beattie (BBB) scale to assess postoperative locomotor activity.

Methods: Rat spinal cord glioma models were created by implanting F98 rat glioma or 9L rat gliosarcoma cells into the intramedullary spinal cord at the Thoracic 9/10 level. BPA was administered intravenously, and the biodistribution of boron was compared. Locomotor activity evaluation after the implantation of tumor cells was using the Basso, Bresnahan, and Beattie (BBB) score. In brief, rats were released into an open-field testing area and observed primarily for lower limb movements for approximately 3 min on a 22-point scale, ranging from 0 (no observed hind limb movements) to 21 (plantar parallel to the trunk, good lower limb clearance, gait coordinated, no trunk sway, and tail always up). In addition, neutron irradiation experiments were performed on the F98 rat spinal cord glioma model injected with BPA. The sham-operated group injected with medium served as a control group. The survival time and BBB score were evaluated in both groups to assess treatment efficacy.

Results: In the biodistribution experiment, BPA accumulates into the spinal cord tumor by intravenous administration (i.v.), with the sufficient boron concentrations at 2.5 h after i.v. (F98: 26.6±5.8, 9L: 15.3±4.5 μg B/g). In the in vivo neutron irradiation experiments, significant differences in overall survival time were observed between the untreated group and BNCT BPA i.v. 2.5 h group through the log-rank test, and the decrease of BBB score of BNCT group was significantly suppressed. In addition, no decrease in BBB score was observed in the neutron irradiation experiment on the sham-operated group. Conclusions: These findings suggest that BNCT is effective in the treatment of malignant spinal gliomas. BNCT may become a treatment option for malignant spinal gliomas in the future.

Keywords: BNCT, spinal cord glioma, boronophenylalnine

Macrophages as potential carriers of boron carbide nanoparticles in boron neutron capture therapy

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Boron neutron capture therapy (BNCT) is a targeted type of radiotherapy mainly intended for the treatment of patients with tumors located in hard-to-reach areas such as brain tumors, melanomas, or head and neck cancers. However, the most challenging aspect of successful BNCT is the delivery of boron compounds to tumor tissue while avoiding significant uptake by normal cells [1]. Following the trend of searching for selective carriers for BNCT, our research team focuses on testing an innovative strategy based on using macrophages as cellular carriers of boron-rich compounds. The application of these cells as nanoparticle carriers in anticancer therapy is becoming increasingly significant mainly due to their natural ability to engulf foreign particles, biocompatibility, non-immunogenicity, long circulation half-life, ability to cross biological barriers, as well as migrate and accumulate at the site of the tumor [2].
To obtain selective cellular boron carriers, the potential of murine macrophages originating from cell lines and bone marrow-derived macrophages to interact with two boron carbide preparations differing in physicochemical properties, especially nanoparticle size was investigated. First, the effect of boron carbide preparations on cell viability, apoptosis induction, cell cycle and cytokine production was assessed. Then, the interaction and uptake of boron carbide nanoparticles by these cells was determined. Additionally, the ability of macrophages loaded with boron carbide nanoparticles to migrate towards the tumor microenvironment was evaluated in vitro. Our studies showed that the sensitivity of cells to boron carbide preparations depended on their origin and the state of polarization in the case of bone marrow-derived macrophages. However, the boron carbide preparation containing larger nanoparticles interacted more with all tested macrophages, which was associated with significant toxicity and production of pro-inflammatory cytokines and impairment of the macrophages' ability to migrate. Therefore, boron carbide containing smaller nanoparticles is more promising for further research, not only due to its lower toxicity to macrophages, especially those derived from the bone marrow but also its significant uptake by these cells and no effect on their migratory abilities. Importantly, bone marrow-derived macrophages are particularly attractive to us as primary cells because they provide a more accurate model of in vivo macrophage physiology than those derived from cell lines.
In conclusion, our research confirmed that the use of macrophages as boron carbide carriers is a promising therapeutic strategy for potential use in BNCT, which may become a new type of radioimmunotherapy.

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Keywords: macrophages, cellular carriers, boron carbide

A platform for quantitative mapping of boron uptake and microdistribution in a preclinical cancer model to inform boron neutron capture therapy (BNCT) drug studies

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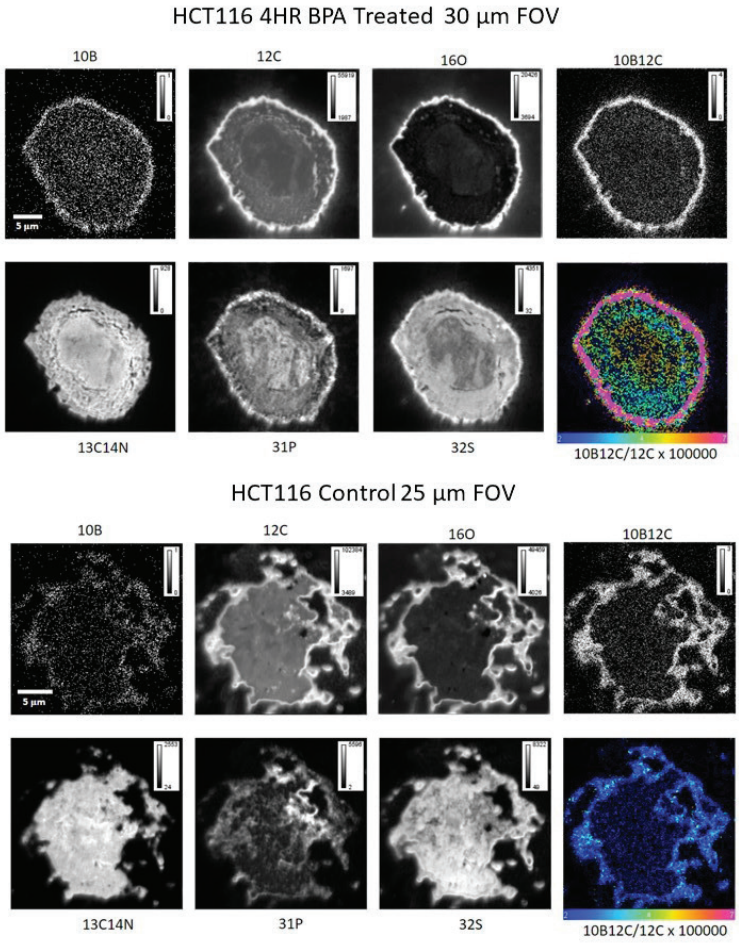

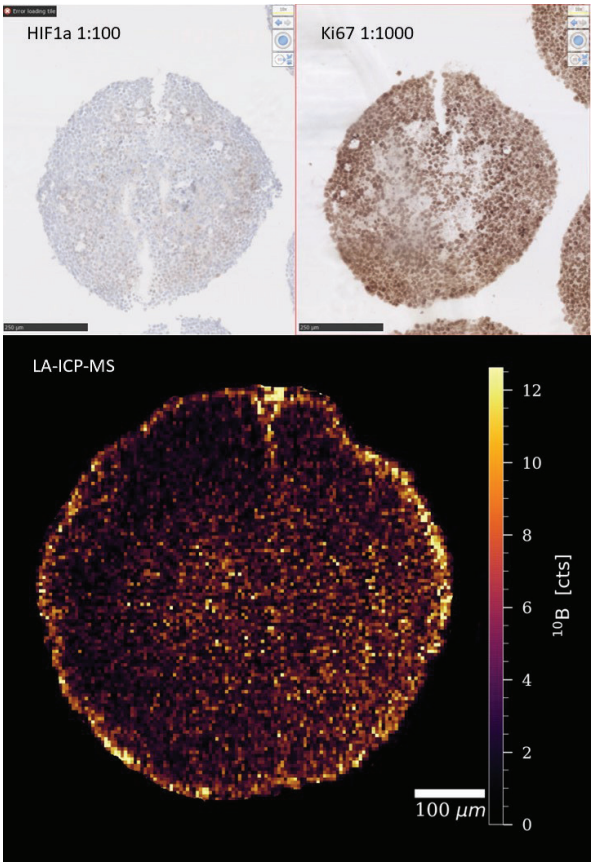

Figure captions: 1-The counts per second of different elements from HCT116 in NanoSIMS analysis 2-Mapping spheroids in LA-ICP-MS analysis using consecutive slide stainings with Ki67 and HIF1a to define cell status

Boronophenylanine (BPA) – the most common clinically used boron agent – is actively transported into tumour cells mainly through L-type amino acid transporter (LAT1), which is present on the cell membrane of various malignant tumour cells. It is widely regarded that the ^{10}B microdistribution and intracellular uptake concentration in current clinical practice is not optimised, with many efforts towards optimisation of delivery of the available drugs, and development of next-generation boron drugs (1). Towards understanding the impact of drug and cell features on BPA uptake and microdistribution, we have developed a preclinical spheroid platform that can map intracellular and intraspheroid localisation of ^{10}B and co-localise them with cell/tumour heterogeneity features. HT29 and HCT116 colorectal cancer spheroids of the diameter of 665 ± 20 µm were developed to recapitulate hypoxic/normoxic and proliferative/quiescent zones within colorectal cancer metastases. These spheroids are highly reproducible, and their sizes and the spatial distribution of cell statuses can be controlled by varying the cell seeding numbers and culturing times. The spheroids were treated with clinical-grade ^{10}B-BPA with a concentration of 1000 µg/mL, and the ^{10}B uptake and microdistribution both intracellularly and within the spheroid were meticulously analysed. Our optimized cryo-fixation and cryo-sectioning pipeline ensured the preservation of cell morphology and precise ^{10}B localisation. Nanoscale Secondary Ion Mass Spectroscopy (NanoSIMS) was employed to spatially resolve and semi-quantify ^{10}B isotopes within clinically relevant detection limits (ppb) and high spatial resolution

(35 nm) intracellularly. A Cs^+ primary ion beam with a 16 keV energy and a current beam of 0.5-2 pA was used for the analysis. Concurrently, other isotopes ($^{12}C^{14}N$, and ^{31}P) were mapped to delineate cellular matter cell structure and nuclei respectively; cell organelles have different concentrations of different elements, e.g., the nucleus has a high phosphorus concentration due to the high ^{31}P content of the DNA phosphate backbone. Consecutive sections of the same spheroid were stained with Ki67 to visualise proliferating cells and HIF1α to visualise hypoxic cells, in addition to scanning electron microscopy (SEM) to facilitate the identification of cell morphology and selection of regions of interest (ROI) for NanoSIMS. The ROIs field of view had a range of area of 25 x 25 μm^2 to 50 x 50 μm^2. Furthermore, laser ablation inductively coupled mass spectrometry (LA-ICP-MS) was employed to delineate the intraspheroid ^{10}B distribution across proliferating and quiescent cells. A laser power of 0.6-0.7 J/cm^2 ablated the whole area of spheroid sections, with a spatial resolution of 5 µm – with the potential to go down to 3 µm – which was then overlayed onto a widefield image to identify cell status. The mean BPA uptake within the spheroids was quantitatively measured using inductively coupled mass spectrometry (ICP-MS), with the capability to detect ^{10}B concentrations as low as 0.2 ppb. We found that NanoSIMS accurately mapped ^{10}B distribution within HT29 and HCT116 cells, yielding average signals of 4.4 ± 0.9 cps and 4.0 ± 0.2 cps respectively, significantly higher than the control values of 0.9 ± 0.5 cps and 0.7 ± 0.1 cps, respectively ($p<0.001$). The two cell lines yielded no significant difference in ^{10}B uptake ($p=0.061$), which is in agreement with the results from ICP-MS. Our platform enables comparison of ^{10}B uptake across different cell lines potentially mapping normoxic/hypoxic and proliferating/quiescent zones, and the plotting of uptake penetration profiles within cell-dense spheroids. This drug uptake and mapping platform unveils the impact of boron drug features, incubation parameters, and cell/tumour characteristics on ^{10}B microdistribution and uptake concentrations, providing insights into optimized BNCT drug solutions. Our future work is to co-localise intratumoural ^{10}B microdistribution with downstream biological response post-neutron irradiation.

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Keywords: NanoSIMS, LA-ICP-MS, BPA, hypoxic, proliferating

Design and optimization of a Beam Shaping Assembly for the BNCT facility based on the RFQ and Be target of the ANTHEM project in Italy

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An Accelerator-Based Boron Neutron Capture Therapy facility will be built at the University of Campania L. Vanvitelli, Caserta, Italy, in the frame of the PNRR-PNC project ANTHEM. A Radiofrequency Quadrupole Accelerator (RFQ), delivering a 5 MeV, 30 mA proton beam, and a beryllium target, have been designed by the National Institute of Nuclear Physics (INFN). This system produces a neutron source of 10^{14} s^{-1}. A task of paramount importance is to moderate the neutron energy distribution generated by protons on the beryllium target to a spectrum suitable for BNCT treatment.
For the treatment of deep-seated tumors, the optimal neutron beam typically peaks between 1 and 10 keV. This requires a Beam Shaping Assembly (BSA) to filter, moderate and collimate the neutron beam. In the present work, the final structure of the BSA is presented. The new set-up has been implemented on the basis of the prototype previously developed as reported by Postuma et al[1]. This structure was used in preliminary studies for assessing the radioprotection of the facility and to simulate BNCT treatments in patients. Nevertheless, this model needed modification to comply with construction constraints. Furthermore, the design of the beryllium target has been altered in terms of shape and thickness since the initial studies. It is now flat and perpendicular to the proton beam, exhibiting improved performance in both neutron production and mechanical properties. The recently updated IAEA figures of merit (FOM) have been used as the classical criterion for assessing the effectiveness and safety of the beam. However, a novel approach to evaluate the therapeutic potential of the beam has been used to guide the design of the final BSA. This method, based on radiobiological FOM rather than on the physical ones, provides a wider perspective and shifts the focus from the evaluation of the beam itself to its dosimetric performance in the patients. The most advantageous BSA has been obtained through simulations of different geometries and materials by using the MCNP6 software and several tests were carried out to evaluate the best performing set-up, also including construction and mechanical elements. The tested moderating materials were: AlF3 doped with LiF, AlF3, MgF2 and Fluental™, considering realistic geometries and densities based on the sintering experience developed in Pavia. Densified bricks of AlF3 and MgF2 have in fact been obtained by optimizing the powder preparation and the pressure/heating application using a machine designed and built on purpose. Lead was selected to reflect neutrons and Polyethylene was used as the shielding material at different thicknesses surrounding the bulk moderating material. A first filter to lower the fast neutron component is followed by blocks of moderating materials while a second filter was introduced to reduce the component and thermal neutrons. Finally, a second region of shielding materials complete the structure in the final part, which was optimized to collimate the neutron beam. This contribution shows the methods for BSA design and evaluation and the dosimetry in a representative case of BNCT treatment.

References: [1] Postuma, Ian, et al. “A novel approach to design and evaluate BNCT neutron beams combining physical, radiobiological, and dosimetric figures of merit.” Biology 10.3 (2021): 174.

Keywords: BNCT Beam Shaping Assembly

Benchmarking the NCT-WES neutron spectrometer with monoenergetic neutrons and radionuclide neutron sources

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The availability of commercially available, hospital-sized, particle accelerator-based fast neutron sources is drawing an increased interest in Boron Neutron Capture Therapy (BNCT). As recommended by IAEA in its recent volume "Advances in Boron Neutron Capture Therapy" (2023), the therapeutic neutron field should be characerised in terms of the thermal, epithermal, fast neutron and gamma components. NCT-WES (Neutron Capture Therapy Wide Energy Spectrometer) is one of the neutron spectrometers recommended by IAEA for assessing the fast neutron component. Its energy interval ranges from thermal up to about 10 MeV. Being a single moderator spectrometer, it simultaneously provides the whole spectrometric information and thus is able to operate as a continuous spectrometric monitor. NCT-WES embeds six thermal neutron detectors in a collimated cylindrical moderator with weight of about 35 kg. Overall, NCT-WES mimics a set of six Bonner Spheres, but its response is sharply directional, and it can operate in real time. To achieve a sharply directional response, the sensitive part is shielded with polyethylene and borated rubber in all directions, except in the direction identified by a collimator. This collimating aperture has cylindrical shape and is internally lined with borated rubber. The neutron spectrum is obtained by unfolding the readings of the internal detectors with the corresponding response matrix. As the energy distributions of neutron beams in BNCT extend from keV to a few MeV, NCT-WES was designed to have its maximum resolving power in this domain. The first prototypal spectrometer was calibrated with monoenergetic nutrons from the 3.5 MV Van de Graaff accelerator of NPL (UK) at energies of 71.5 keV, 144.2 keV, 565.1 keV, 841.9 keV and 1200.4 keV. Additional validation experiments were performed at the STUK neutron metrology laboratory (Finland), where two ^{252}Cf and two ^{241}Am-Be radionuclide neutron sources are available. This communication describes the NCT-WES spectrometer and the results of these epxeriments.

Keywords: NCT-WES, single moderator spectrometer, unfolding

First comparison and combination of BNCT and CIRT dosimetry in a head and neck tumor using the photon isoeffective dose model.

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Boron Neutron Capture Therapy is a radiotherapy based on the selective load of ^{10}B in tumor cells and on subsequent neutron irradiation. Low-energy neutrons are captured in boron and the resulting charged particles deposit a highly localized radiation dose. The total radiation field is a mix of different types of charged particles and photons, thus the absorbed dose must be expressed in photon-equivalent units. This work analyzes an adenoid cystic carcinoma treated with CIRT as an example of how to apply the BNCT photon isoeffective dose model and how to evaluate the BNCT dose distribution against CIRT. The patient received CIRT with a dose constraint on the optic nerve, affecting the peripheral part of the Planning Target Volume (PTV). After the treatment, the tumor recurred in this low-dose region. BNCT was simulated for the primary tumor, to calculate the dose distribution in isoeffective units and a Tumour Control Probability (TCP) to be compared with the one of the original treatment. BNCT was then evaluated for the recurrence in the underdosed region which was not optimally covered by CIRT. Finally, a BNCT and CIRT combined treatment was considered to show the consistency and the potential of the model. For the primary tumor, the photon isoeffective dose distribution due to BNCT was evaluated and the resulted TCP was higher than that obtained for the CIRT. The formalism produced values that are consistent with those of carbon ions. For the recurrence, BNCT dosimetry produces a similar TCP than that of primary tumor. A combined treatment was finally simulated, showing a TCP comparable to the BNCT-alone with overall dosimetric advantage in the most peripheral parts of the treatment volume.
Isoeffective dose formalism was proven as a robust tool to analyze BNCT dosimetry and to compare it with the photon-equivalent dose calculated for carbon-ion treatment. This study introduces for the first time the possibility to combine the dosimetry of CIRT and BNCT, showing the potential of exploiting the cellular targeting of BNCT combined with the precision of charged particles in delivering a homogeneous dose distribution in deep-seated tumors.

Keywords: isoeffective dose, Carbon ion therapy,TPS

DNA Damage and Repair Modeling in Boron Neutron Capture Therapy based on Monte Carlo Track Structure Simulations

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Boron Neutron Capture Therapy (BNCT) is a binary targeted radiotherapy based on the 10B(n,α)7Li reaction, generating secondary particles with high cross-section and cell-scale range advantages, resulting in a high relative biological effectiveness (RBE) in tumors. However, there is a lack of theoretical research on the biological effects of BNCT. This study aims to establish a Monte Carlo Track Structure (MCTS) particle transport simulation platform suitable for the BNCT environment. Differential cross-section corrections were applied to low-energy Li -7 ions in Geant4-DNA/TOPAS-nBio. The correction algorithm employed an equivalent charge scaling method and a double-parameter fitting method. Subsequently, the model was used for detailed DNA-scale modeling, and MCTS transport simulations were performed for the physical and chemical stages of radiation action, assessing DNA damage production. The study then simulated and repaired DNA damage based on BNCT scenarios, considering the impact of complex composite biological effects (CBE) leading to multi-particle cooperative effects. Finally, different RBE prediction mechanism models under various biological endpoints were constructed, incorporating a cell repair model that considers multi-particle cooperative effects. In this research, the Geant4-DNA simulation platform was utilized to obtain DNA damage under different doses for Co-60 and 7.5 MeV proton irradiation, showing good agreement between the double-strand break (DSB) yields and experimental values. The obtained damage data served as input for the analysis of DSB repair kinetics, and the resulting repair kinetics curve was consistent with literature experimental data, demonstrating the effectiveness of predicting DSB repair. Additionally, this study reveals that when the intracellular accumulation of the drug surpasses a certain threshold, the influence of the intracellular-to-extracellular boron concentration ratio on RBE diminishes until it disappears. Based on this method, the DNA damage and overall repair conditions for various particles in the BNCT environment were obtained, evaluating the individual radiation biological effects after BNCT treatment. This supports the future development of personalized treatment and bridges the gap between radiation biological effects and physical doses, paving the way for the future of personalized cancer treatment.

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Keywords: BNCT, DNA damage, Monte Carlo

Investigation of the possibility of using the neutron flux of the R7-M accelerator for the purposes of BNCT

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One of the methods of cancer treatment is boron neutron capture therapy (BNCT). Research nuclear reactors and accelerators of various types are used as a source of the necessary epithelial neutron flux for BNCT [1]. Already at the moment, an experimental complex of BNCT has been created at the IRT-T reactor at Tomsk Polytechnic University [2]. In this paper presents the results of an experimental determination of the neutron flux density at the R7-M cyclic accelerator of Tomsk Polytechnic University to justify the use of the BNCT method. To carry out the experiment, the fourth channel of the accelerator was selected, where a deuteron flow with an energy of 13.6 MeV and a current of 45 μA interacts with a beryllium target according to the reaction – $Be^{9}(d,n)B^{10}$. The neutron flux density was measured using activation foils made of Fe, In, Ni. The foils were irradiated for 20-30 minutes at a distance of 7 cm from the target and at the cut of the experimental channel. After irradiation, the foils were kept in a lead container for 24 hours, and then measurements were taken on a "Canberra" multichannel gamma spectrometer. Then the results were processed. As a result, it was found that the total flux density at a distance of 7 cm from the target was $9 \cdot 10^{13}$ neut/cm^2·s with an energy of 1.2-11.8 MeV. In the future, it is planned to carry out calculations in the PHITS and MCU software packages and experiments to determine and place the most suitable moderator (Fluental, AlF_3, D_2O, CaF_3) in the accelerator collimator channel to obtain the necessary characteristics of the neutron flux for BNCT [2].The use of the R-7M accelerator as a source of neutrons for boron neutron capture therapy seems very promising, due to the neutron flux it creates. The creation of a collimator for the accelerator will significantly simplify access to this type of treatment for people with cancer.

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Keywords: BNCT, accelerator, neutron flux

Does including the dependence of the biological effect on the energy of charged particles in photon equivalent dose models significantly affect dosimetry in BNCT?

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$$D_R(D_1,\dots,D_5) = \frac{1}{2}\frac{\left(\alpha/\beta\right)_R}{G_R}\left(\sqrt{1+\frac{4G_R}{\alpha_R\left(\alpha/\beta\right)_R}\left(\sum_{i=1}^{5}\sum_{k=1}^{N_i}\alpha_i(E_{ik})D_{ik}+\sum_{i,j=1}^{5}\sum_{k=1}^{N_i}\sum_{l=1}^{N_j}G_{ij}(\theta)\sqrt{\beta_i(E_{ik})\beta_j(E_{jl})}D_{ik}D_{jl}\right)}-1\right) \quad (1)$$

Index i (or j) indicates the particle type. For each type of particle i, N_i is the number of energy bins, E_{ik} the k-th energy (with $1 \le k \le N_i$), $D_{i,k}$ the dose imparted by particles with energy E_{ik}, $\alpha_i(E_{ik})$ and $\beta_i(E_{ik})$ the alpha and beta coefficients of particle type i with energy E_{ik} and G_{ij} the Lea-Cacheside time factor.

The biological effect of radiation is known to depend not only on the absorbed dose but also on the type and energy of the charged particles delivering the dose. Existing models in Boron Neutron Capture Therapy (BNCT), which convert the absorbed dose into an equivalent dose of photons, seek to incorporate the dependence of the biological effect on the radiation type. This is achieved by considering the primary uncharged particle fields under the Charged Particle Equilibrium assumption. The contributions of the total absorbed dose are then weighted with different experimental relative biological effectiveness factors (as in the fixed-RBE dose model [1]), or by assigning different alpha and beta parameters derived from the Linear-Quadratic survival model (as in the photon isoeffective dose model [2]). The lack of inclusion in current models of the dependence of the biological effect on the energy of secondary charged particles – exemplified by the use of the same RBE or radiobiological parameters for both the case of monoenergetic protons released during thermal neutron capture on nitrogen and the multi-energy recoil protons resulting from elastic collisions of fast neutrons- prompted our investigation into this matter. Specifically, our study was conducted in the context of one of the most critical treatment targets in BNCT: head and neck cancer. Focusing on a patient with squamous cell carcinoma (SCC), we simulated the corresponding BNCT treatment involving a single irradiation with an epithermal clinical beam directed at the tumor. The main secondary charged particles released by thermal neutron capture reactions in tissue with B-10 are protons, alpha particles, Li-7 and C-14 ions and electrons. To account for the dependence of the biological effect on both the type and energy of these particles, which are the real causes of radiation damage to DNA, we reformulated the photon isoeffective dose model presented in [2] as in Eq. 1.
For the treatment simulation, the MultiCell model of the patient was coupled with the PHITS transport code. Within three regions of interest in the tumor, covering proximal and distal positions along the central axis and one off-axis position, we obtained the necessary estimates required by the expression (1):
a. the total absorbed dose for each particle field (T-deposit),
b. the absorbed dose of protons as a function of the initial kinetic energy (T-deposit),
c. the recoil proton spectrum (T-product),
d. the probability distribution of Linear Energy Transfer (T-LET).
The biophysical model BIANCA [3] was used to derive alpha and beta coefficients for SCC cell survival as a function of the LET for protons, particles and Li-7 and C-14 ions. In the case of photons, single- alpha and beta coefficients were determined from Co-60 experimental data. The LET distributions obtained from PHITS for each type of radiation were used to compute the radiobiological parameters of expression (1), in accordance with the predictions of the BIANCA model for the SCC cell line. The extended formalism was then applied to calculate photon isoeffective doses for a typical BNCT irradiation. The dependence of the results on the variation of the neutron spectrum according to the studied positions in tumour was investigated. Finally, the implications of considering the dependence of the biological effect on both the type and energy of the secondary particles in the photon isoeffective dose calculations are discussed.

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Pharmacokinetic modelling to extrapolate from mouse to human biodistribution data for new tissues and compounds

Warren Kilby[1], Chad Lee[1], Michael Torgov[1], Tioga Martin[1], Linette Capo[1], Maki Ikeura[1], Maria-christina Malinao[1], Karen Morrison[1], Kendall Morrison[1]
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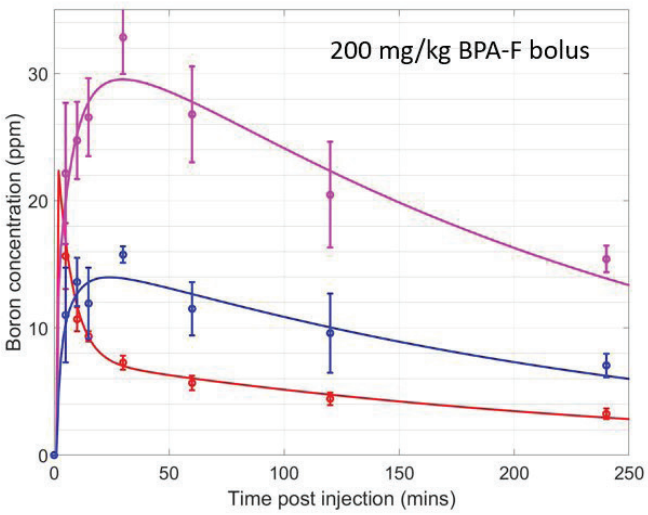
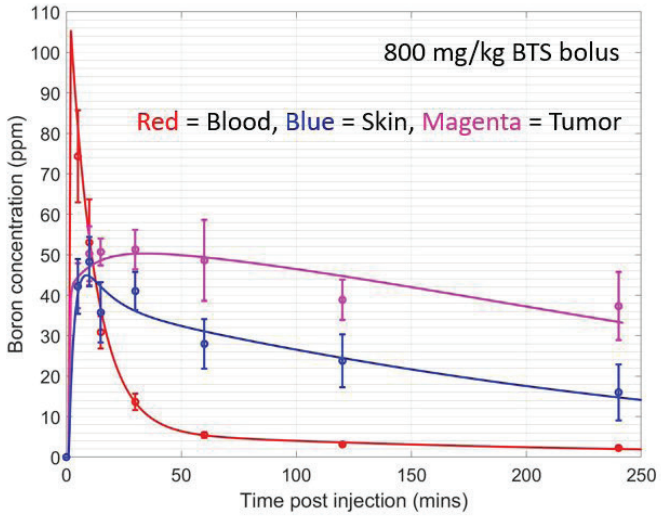
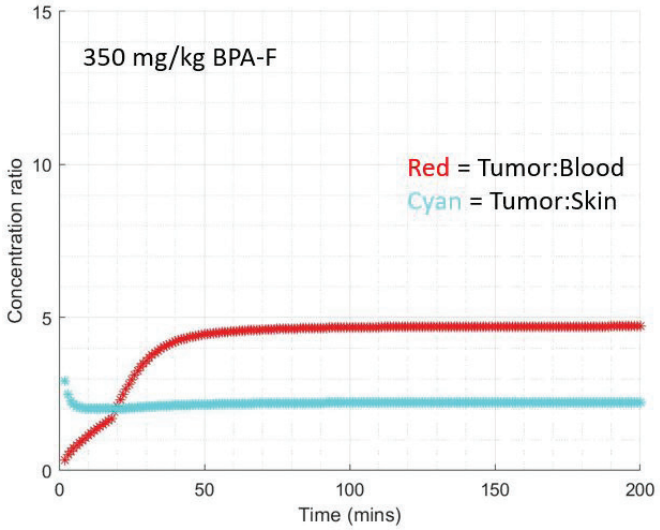




Parameter	Model prediction after 350 mg/kg BPA-F infusion in human	Reference human values
Blood boron concentration	15 ppm	15 ppm
Tumor:Blood boron concentration ratio	3.3	3.5
Skin:Blood boron concentration ratio	1.6	1.4 [5]



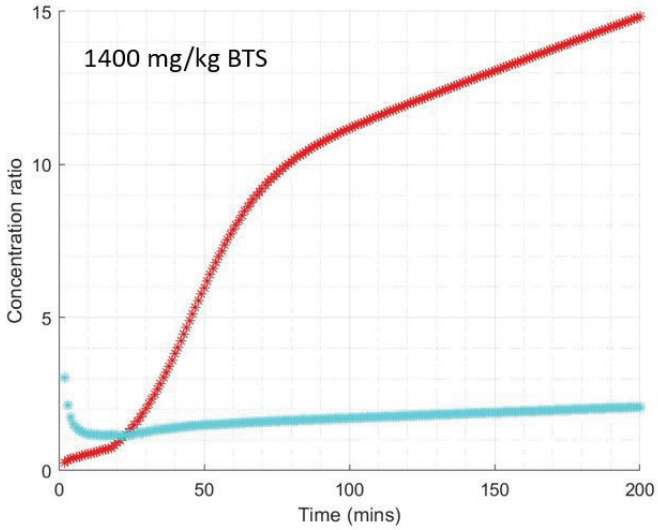


Figure captions:
Fig 1. Mouse biodistributions after bolus injection
Table 1. Model predicted concentrations in human
Fig 2. BPA-F vs. BTS 90-minute human infusions scaled to mouse-time

In the absence of real-time measurement, tissue boron concentrations are estimated using pre-treatment blood measure-

ments and pharmacokinetic (PK) modelling to extrapolate to time of treatment. Models have been validated for BPA-F in a small range of tissues. These models might also be used to fit boron biodistribution measurements in animal models for tissues and compounds where human data doesn't yet exist, from which equivalent human distributions can be estimated by allometric scaling. These results can guide candidate selection for drug development and provide initial estimates of clinical utility using treatment plan evaluation before human data is available.
We implemented a 2-compartment model for blood [1] and a modified closed 3-compartment model for tumor and healthy tissue [2]. This second model describes the response function of a secondary tissue compartment to an impulse in the blood compartment and is solved as a convolution with the result of the first step. We formulated the convolution as a definite integral and solved analytically. Parameter optimization used the Levenberg-Marquardt method implemented in Matlab (Mathworks Inc., MA). We evaluated the fit accuracy in human blood using published data from 16 patients with BPA-F doses of 77 – 330 mg/kg infused over 35 – 180 minutes. All measurements made until 60 minutes post-infusion were used to fit the model, which was then used to predict blood concentration for the subsequent 30-60 minutes. The median absolute agreement between prediction and measurement during the first 30 minutes was 3.5%, increasing to 5.3% over 60 minutes. Acquiring additional measurements post treatment significantly improved the modeling accuracy, allowing retrospective fine-tuning of the delivered dose estimate.
We then fitted the models to measurements from a mouse xenograft model with a human squamous cell carcinoma nasopharyngeal cancer cell-line (FaDu) after bolus injection of BPA-F [3]. The model enabled prediction of boron concentrations after continuous infusion rather than bolus injection. To convert between mouse and human we used allometric scaling [4]. The mouse blood boron concentration after bolus injection was compared to the model prediction using average human parameters. The units of time and concentration were scaled to compensate for differences in metabolic rate and volume of distribution between the two species until the agreement was optimized. A time scale-factor of x7 (1 mouse-minute = 7 human-minutes) provided good agreement over the first 30 mins of mouse-time which is very similar to the ratio of basal metabolic rates per unit bodyweight. The scale factors established with blood were applied to the mouse model for tumor and other tissues. Simulating the response to a human BPA-F infusion schedule using the scaled mouse model yielded tumor and skin concentrations that were in good agreement with published human values (Table 1).
Finally, the PK model was fitted to mouse data acquired with the novel boron delivery compound boronotyrosine (BTS) which has both significantly higher solubility and tumor:blood ratio after bolus injection than BPA-F [3]. Figure 1 shows that the model fits well to this novel compound. The allometric scaling factors obtained with BPA-F were then applied to estimate the concentrations following a human equivalent infusion schedule (Figure 3). Using the same scale factors for both compounds is a significant assumption that must be validated experimentally, but it should be noted that BPA and BTS are amino acid analogs that are transported by the same LAT-1 mechanism [3]. These results suggest that BTS achieves a tumor:blood ratio of 12:1 for the same tumor:skin ratio after infusion, and treatment planning has shown that this allows head and neck tumor dose to be increased >2x compared to BPA-F while respecting dose constraints to skin and mucosa [6].

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Keywords: BPA, boron compounds, BTS

478 keV gamma photons measurement in determining of therapeutic effects in BNCT

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Short ranges of α particles of the order of μm, its high LET and RBE make the particles clinically useful in terms of effectiveness of radiotherapy1. An example of the α particles using therapy is Boron Neutron Capture Therapy (BNCT), which is currently the object of the growing interests due to its promising perspectives for radiotherapy difficult to treat malignancies. During the BNCT the boron compound is given to the patient who is also receiving radiation coming from neutron beam. The advantage of the BNCT is selective destruction of cancer cells with limited damages to normal cells. The selectivity of the damages is conditional on degree of absorption selectivity of the boron compound by the cancer cells, where the α particles from 10B(n,α)7Li reactions occur. However, bimodality of the therapy presents many difficulties. Firstly, there is the problem of achieving sufficiently selective boron compound to the cancer cells. Secondly, there are difficulties getting appropriate parameters of neutron beam. Thirdly, the adequate real-time dosimetry system during the irradiation for the creation of the appropriate treatment plan is needed. The last one is bound to the first two and determines therapeutical effect and allow assess the damages to normal cells2. It is not possible to measure directly the α particles in a body during the treatment due to its short ranges in a tissue. However, α particles from 10B(n,α)7Li reaction can be indirectly measured by 478 keV γ photons measuring. The 478 keV γ photons are produced in the same reaction with a probability of 94% and their quantity is proportional to the dose deposited by the α particles. It is important to note, that undesired dose coming from primary and secondary radiation should not be neglected. Furthermore, to precisely measure the alpha particles the adequate experimental set-up for the purpose should be tested and used. During the session the experimental set up built for the purpose of the measurements carried out at the National Centre for Nuclear Research in Świerk, Poland and the preliminary results of 478 keV gamma photons measurements as a substitute for α-particles dosimetry will be presented. The main challenges and difficulties encountered during the study will also be discussed3.

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Keywords: BNCT, 478keV gamma, photon, alphaparticle

Characteristic measurement for the neutron beam of iBNCT001, a linac-based BNCT device from Tsukuba

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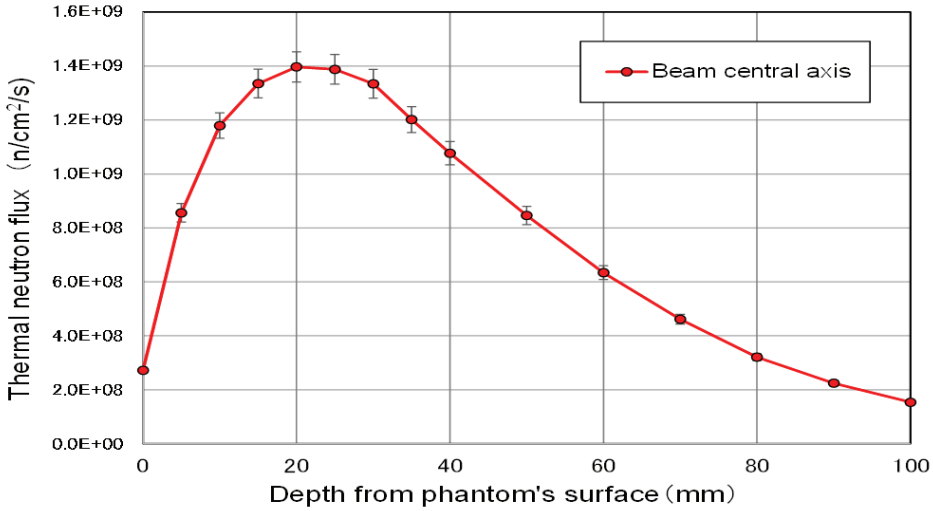

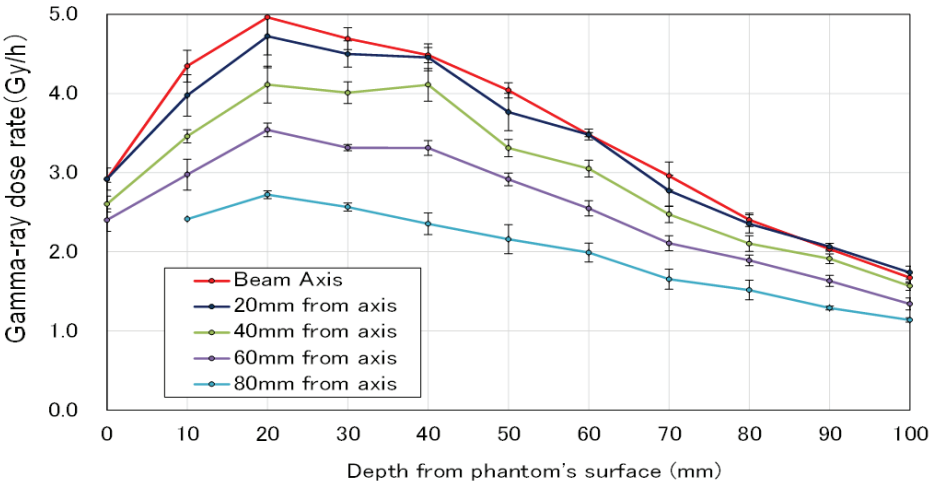

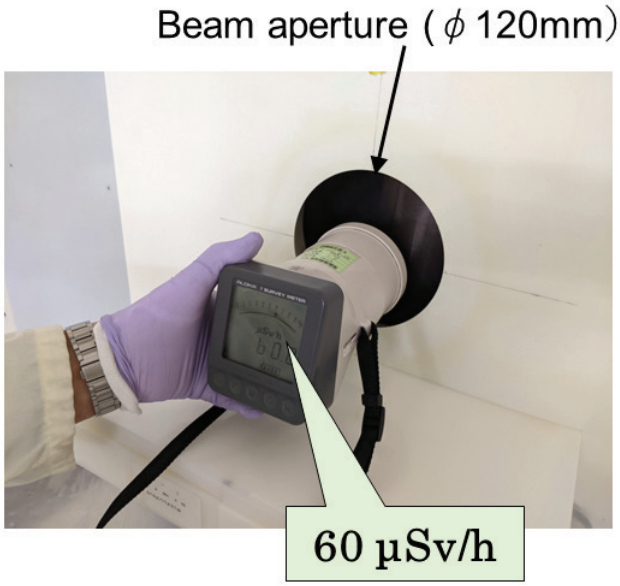

Figure captions:
Fig.1 Thermal neutron flux distribution on beam's axis
Fig.2 Distributions of gamma dose rate in water phantom
Fig.3 Measurement of residual gamma-ray around beam port

[Introduction] iBNCT group headed by University of Tsukuba has produced "iBNCT001" as the demonstration device of the linac-base neutron source for BNCT [1]. For the proton accelerator, the device has adopted a linac formed an RFQ and a DTL type, protons of the average current of approximately 2 mA are accelerated using the linac to 8 MeV. For neutron target material, beryllium has been combined. Thus, iBNCT001 generates high-intensity neutrons by irradiating the 8 MeV proton beam to the beryllium target. An epithermal neutron beam which is generated by passing through the BSA is released from the beam aperture. We plan to use this device to conduct clinical trials on first malignant brain tumors. Prior to this clinical trial, we had to validate therapeutic applicability and safety of the neutron beam of the device. Thus, various physics measurements of the epithermal neutron beam released from the beam aperture were performed [2].

[Methods] To understand dose distribution in a patient's head when the neutron beam is irradiated to a patient, we have performed neutron irradiation experiments using a rectangular water phantom. Two-dimensional distributions for thermal neutron flux and gamma dose rate in the water phantom have been measured since both radiations are fundamental factors in estimating dose in BNCT. The stability and lifetime of the beryllium target have also been evaluated. Furthermore, leakage radiation out of the irradiation field and residual radiation after treatment irradiation were measured, respectively. In the measurement of the leakage radiation, detectors for thermal neutron and gamma-ray were set on various positions on the whole-body phantom such as neck, breast, and abdomen, and then the epithermal neutron beam was irradiated to the head part of the whole-body phantom. In the evaluation for residual radiation, we measured gamma dose around the beam aperture 15 minutes after the normal phantom irradiation experiment finished.

[Results] In the measurement of the thermal neutron flux, the peak of thermal neutron flux in the phantom was approximately 1.4×10^{9} ($n/cm^2/s$) at a depth of 20 mm from the surface. The maximum dose rate of gamma dose rate was approximately 4 Gy/h at the same point of the peak thermal neutron flux. Fig.1 shows the thermal neutron flux distribution on the beam's axis. The gamma-ray dose rate distribution on the beam's axis is shown in Fig.2. Based on these measurement results, we conducted a dose evaluation. The neutron beam can generate a therapeutic dose to a depth of 6 cm or more in a head. For the stability and lifetime of the beryllium target, we confirmed that one beryllium target can generate a constant intensity of neutrons stably against more than 1,000 irradiations. In the evaluation of residual radiation 15 minutes after the normal irradiation, it was confirmed that the value of residual gamma dose around the beam port was less than 60 μSv/h. Fig.3 shows the measurement of residual gamma dose around the beam port. This value is low enough for the therapeutic equipment of BNCT. Therefore, medical staff can approach a patient immediately after irradiation and conduct various procedures.

[Conclusion] The measurement results prove that iBNCT001 can release a neutron beam applicable to BNCT treatment. Our group has also conducted non-clinical studies with neutron irradiation of various cells and mice. The results also demonstrated biologically that the beam can be applied to irradiation with a human. The protocol of the clinical trial was agreed with PMDA and was also reviewed by the Institution Review Board. The protocol and applying iBNCT001 to clinical study have been just approved. We will finally conduct the phase 1 clinical trials of malignant brain tumors in early 2024.

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Keywords: BNCT, neutron beam, physics measurement

Real-Time Boron Concentration Measurement in BNCT Using Compton Imaging

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Dosimetry in BNCT poses significant challenges due to the indirect effect of neutrons interacting with elements within the body and uncertainties associated with the uptake of boron compounds used in clinical practice. Current treatment planning relies on unconventional estimates of boron tumor uptake derived from prior PET scans and thus, an online boron-uptake monitor would be highly convenient.
This contribution presents first pilot experiments carried out at ILL-Grenoble with a high-efficiency Compton camera, hereby aiming at demonstrating BNCT dosimetry by introducing real-time measurement and imaging capabilities for boron concentration. For this experiment, cancer cells of tongue squamous cell carcinoma, malignant melanoma and glioblastoma were prepared with different ^{10}B concentrations, ranging from 100 ng up to 100 µg, as well as control samples of the same cancer-cell lines without any boron intake. In addition, samples with known ^{10}B mass in the same range were produced to provide an absolute calibration for the quantitative measurement of the Boron concentrations.
The samples were irradiated with the thermal neutron spectrum at the FIPPS experimental station at ILL-Grenoble. The 478 keV gamma-rays from the ^{7}Li de-excitation after the ^{10}B(n,alpha) neutron-boron reaction were registered both with the Compton imager and the FIPPS HPGe array installed at ILL. The latter is a well established setup that is commonly used for PGAA measurements and was used as the reference detector to benchmark the performance of the Compton imager.
The measurements performed at ILL allowed us to demonstrate the imaging capabilities of the Compton imaging device for this type of application, address its overall performance and capability to quantitavely monitor the ^{10}B(n,alpha) reaction rate over a wide range of 10B concentrations similar to that of actual BNCT treatments. This experiment also served to determine the sensitivity of the Compton imager, which was found to be below 1 µg of ^{10}B. A summary of the experiment, preliminary results and future prospects of this project will be presented in this contribution.

Keywords: Dosimetry, gamma-ray imaging, Compton, ILL

Treatment planning of boron neutron capture therapy for hard-to-treat recurrent breast cancer

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Treatment planning system THORplan [1] has been use for clinical trial of boron neutron capture therapy (BNCT) since August 2010 under collaboration with Taipei Veterans General Hospital for recurrent head and neck cancer. Its use of other indications such as hard to treat breast cancer is investigated in this study under the collaboration with Taichung Veterans General Hospital. The first thing to do is to set up the dose constraints for organs at risk. The 2nd thing to do is to find the CBE for lung and liver which will usually be inevitably irradiated during the treatment. The dose limit for skin is 15 Gy-W, for aorta is 8 Gy-W. Other dose constraints of organ at risk for photon therapy can be found in NSABP B51/RTOG 1304 [2]. Organs at risk include Ipsi-lateral lung, contralateral lung, heart and contralateral breast. These dose constraints were converted to biological equivalent dose (BED) for BNCT. The CBE for lung is 2.3 [3], for liver is 4.25 [4]. The blood boron is assumed to be 30 ppm and ratio of boron in tumor to normal tissue is set to be 2.5.
Several incident directions are tried to match the clinical requirements. It is possible to deliver average dose of ~30 Gy-W to the tumor, under the skin and heart dose constraints. The dose limiting organ is heart. The use of bolus is helpful in reducing the doses of most normal organs such as heart, lung and aorta, except that skin dose is slightly increased under the same average dose to the tumor. The dose limiting organ is skin. By using bolus the mean heart dose can be reduced by 40%. The ipsilateral lung dose can be reduced by 20%. The liver dose can be reduced by 40%. The aorta dose can be reduced by 20%. The irradiation time can also be reduced by 20% to ~ 45 mins under the 1.2 MW power of THOR reactor.

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Keywords: BNCT, treatment planning, breast cancer

On the role of standardisation of n-γ beam phase space data for Monte Carlo based tools

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With the recent development of accelerator-based BNCT facilities in operation or soon to be in operation, there is a need to establish standards in many areas for clinical application and research around them. Since many experimental and numerical studies need to be performed in the field of beam quality, patient dose and radiation safety assurance, it seems reasonable that numerical data (eventually validated data) of the phase space distribution for RB-BNCT and AB-BNCT facilities should be collected in an open database and disseminated within the BNCT community.
According to IAEA [1], the phsp data is defined as a collection of representative pseudo-particles emitted from a radiotherapy treatment source together with their properties, which include energy, particle type, position, direction, progeny and statistical weight. Each pseudoparticle in the phsp should be scored so that it is recorded only once as it passes through the scoring surface. This depends on the detailed description of the phsp particles, i.e. phsp variables as generated by a Monte Carlo simulation of the treatment source, or the form of a computer code that simulates the treatment source using either a full Monte Carlo simulation or a beam model of the radiation therapy source.
Therefore, we would like to address this issue and, using the exemplary IAEA PHSP database, present a numerical Monte Carlo intercomparison based on phase space data within four well-known Monte Carlo codes, viz: MCNP [2], PHITS [3], FLUKA [4] and GEANT4 [5].
For these studies, we used a numerical model of the MARIA research reactor core and the H2 neutron facility at the H2 horizontal channel, which is currently being commissioned. We would like to present the whole process of preparation and conversion of the numerical models between Monte Carlo codes, as well as the comparison of the results, including neutron and gamma spectra, absorbed doses and dose equivalents at selected reference points located in the rooms of the H2 neutron laboratory.

Acknowledgments
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Keywords: Monte Carlo, phase-space data,

Experimental and computational approaches to develop a Photon Isoeffective Microdosimetric Dose Model for glioblastoma multiforme in BNCT

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In BNCT, the determination of absorbed dose within a tumor has conventionally relied on the computation of the Kinetic Energy Released in Matter (KERMA). This approach operates based on the assumption of charged particle equilibrium and, consequently, assumes a homogeneous distribution of boron throughout the entire tumor volume at both spatial macroscopic and microscopic levels.
Some evidence has emerged, indicating the presence of heterogeneity in the distribution of boron within tumor cells. Under the assumption that the tumor is modeled as a closely packed collection of cells, this study focuses on the integration of microdosimetric aspects into the Photon Isoeffective Dose Model for glioblastoma multiforme (GBM).
The Photon Isoeffective Dose Model translates the BNCT absorbed dose to photon-equivalent units equating a desired effect [1]. Calculating KERMA with the assumption of a uniform boron concentration may result in an overestimation of the absorbed boron dose. Hence, the importance of conducting a more detailed calculation by implementing microdosimetry. In [2], an analytical formalism is presented to describe the stochastic dose distribution arising from non-uniform boron microdistributions in microscopic biological sites. In particular, for the correction of the administered macroscopic doses in GBM, we focus on the determination of the microscopic dose correction factor introduced in [2] (referred to as “eta factor”), which depends on the shape and size of the site of interest, the microdosimetric magnitude intrasite frequency mean specific energy, the ratio of reaction rates inside and outside of the site and the total average energy per reaction.
The eta factor was calculated for a bi-valued boron microdistribution, where the rate of reactions differs inside and outside the cell nucleus, but remains uniform in each region of interest. Using the Monte Carlo code PHITS, the cell nucleus was modeled as a spheroid and the spectrum of energy deposited within it was calculated for the expected relation between the boron concentration in the nucleus and the cytoplasm in a GBM cell. From the simulation output, the specific energy spectrum and the intrasite frequency mean specific energy, zFI were obtained.
As pointed out above, the computational model in PHITS needs to be supplied with the best estimate of the boron microdistribution at the cellular level. For this purpose, the boron microdistribution in the U87 cell line, representative of glioblastoma multiforme, was calculated using the neutron autoradiography technique.
Neutron autoradiography is a methodology based on the use of a Nuclear Track Detector (NTD) that allows correlating the microdistribution of boron in a biological sample with the damage (“nuclear tracks”) produced by the particles from the BNC reaction, which are recorded on the detector. In [3] the imprint formation of biological material on polycarbonate nuclear track detectors by UV-C exposure was studied to simultaneously visualize cell imprints and nuclear tracks.
The U87 cells were cultured on polycarbonate detectors and incubated for 4 hours with BPA (80 ppm). Once fixed, the assembly “cell culture+NTD” was irradiated at the RA-3 reactor of the Ezeiza Atomic Center, Buenos Aires, Argentina, with a neutron fluence of 1012 n cm-2. After staining the cells with eosin (15 s), the assemblies were exposed to 5 min of UV-C (254 nm). The imprints and tracks were revealed by a chemical etching with a KOH solution (70°C, 4 min). Cell nucleus, cytoplasm and nuclear tracks were segmented on microscopy images (100x).
Following the procedure outlined in [3], the boron microdistribution within GBM cells was determined. Based on PHITS estimates for the obtained relation of the boron concentration in the nucleus and the cytoplasm, the microscopic dose correction factor was calculated and used to estimate the dose delivered to a patient with the IsoeffectiveModel.

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Keywords: PhotonIsoeffectiveDoseModel, Neutron-Autoradiography.GBM,Microdosimetry

First experimental test of neutron production from 7Li(p,n) at 2.1 MeV and the MgF2 moderating capabilities for the BSA design of the NeMeSis project for BNCT.

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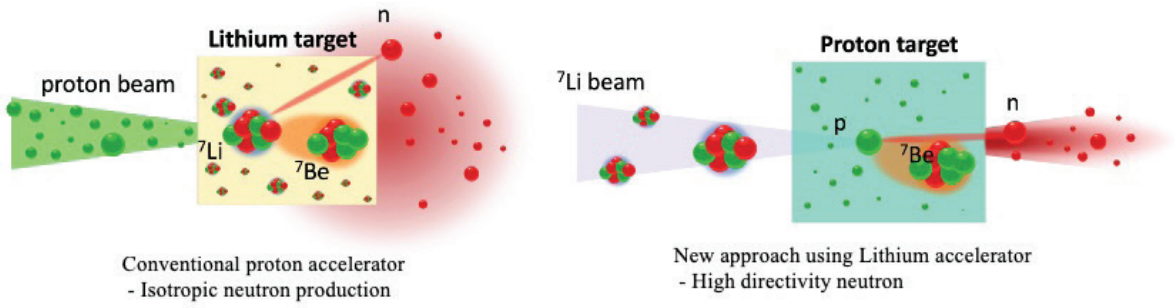

Figure 1. Isotropic and Inverse kinematic focusing

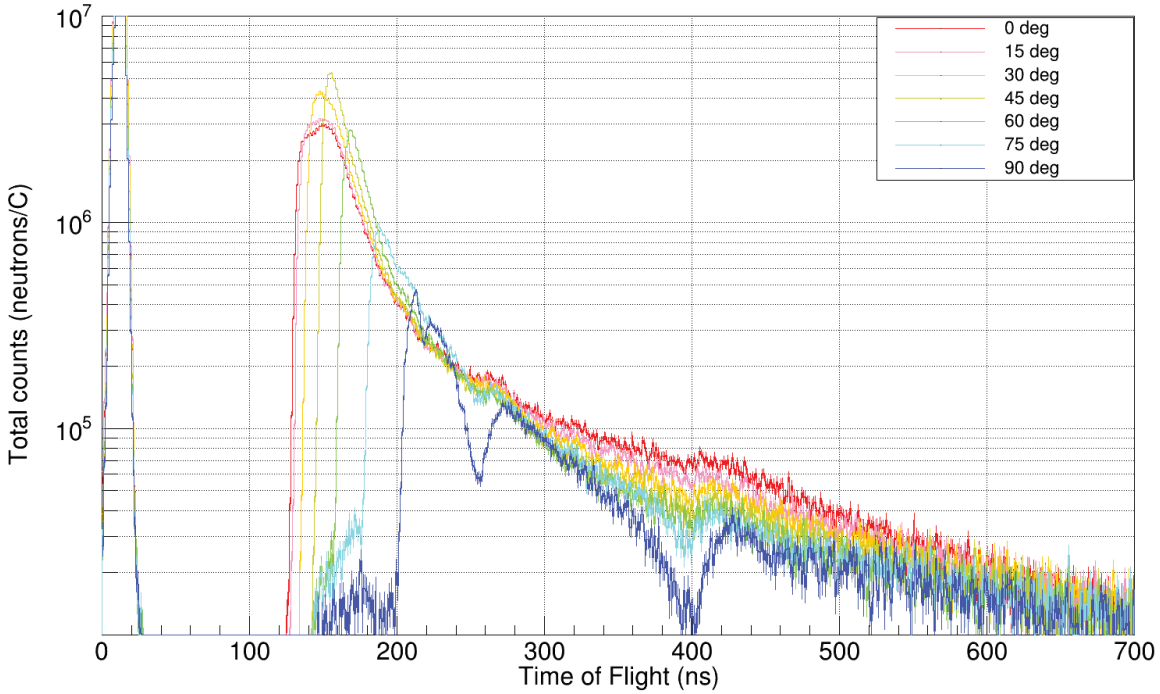

Figure captions:
Graphic 1: Experimental set up pf the MgF2 blocks to test their moderation capabilities.
Graphic 2: Experimentally measured Time Of Flight spectra of the irradiated LIF target at a flight path of 1m.

In the frame of the NeMeSis project at the University of Granada, we are working on the design of a neutron beam with a suitable energy spectrum of neutrons for the irradiation of patients. In order to deliver a high quality neutron beam, with low fast neutron contamination and complying with the recommended figures for BNCT treatments [1], the NeMeSis project from the University of Granada has drafted a model of a Beam Shaping Assembly (BSA), coupled to a proton accelerator working at low energy (2.1 MeV) to produce neutrons by the 7^Li(p,n)7^Be reaction [3]. The BSA is composed of several parts, where the core of the moderating capabilities are focused on a series of blocks made of MgF2 (Graphic 1).

In order to obtain a first run of validation of the sound results of the BSA design coming from simulations with MCNP, a series of experiments have been performed. This set of experiments includes 1) a validation of the neutron yield produced by accelerating protons at 2.1 MeV onto a Lithium target (which was based in analytical calculations during the design of the BSA, though it is well known near the threshold) [3]; 2) measurement of the total cross section of Mg and F through transmission (as there is lack of experimental data from some cross-sections of magnesium isotopes at energies of interest for BNCT); and 3) measurement of the neutron spectra coming out of a sizeable block of MgF2 to test their moderation capability.
The experiment was performed at the MONNET facility of the Joint Research Centre (JRC) in Geel, Belgium, which comprises a TANDEM accelerator and a very clean, low-background experimental area, specially devised for high quality measurements [4]. All experiments were performed using the pulsed mode in the accelerator, in order to profit from the Time Of Flight (TOF) technique to obtain the neutron spectra. A LiF target was irradiated with 2.1 MeV protons, and a set of detectors including a Lithium glass detector (for measuring the neutron spectra), a CeBr3 detector (for measuring gamma production) and a Long Counter (to collect information about the total current received, i.e. normalization). Neutron spectra were measured at several angles covering from 0 to 90 deg and at a flight path of 1 m for the lithium source validation (Graphic 2). Several Mg and MgF2 samples of various thicknesses were used to obtain the transmission spectra (at a flight path of 2 m to increase the resolution), and a larger block of MgF2 made of sintered pieces (4 cm thick and 15 cm in diameter) was used to test the moderating capabilities of this material, also by measuring the TOF spectra at 1 m and the same angles from 0 to 90 deg.
These measurements offer not only an important as a first experimental check of the BSA model developed at the University of Granada, but more broadly, a general result in the form of Mg and F isotopes cross-sections in the keV range, that can be useful for designing accelerator-based neutron sources with MgF2 as moderator. These measurements will allow to validate the simulated results and constitute a key step ahead towards the building and implementation of BNCT facilties in the medical environment.

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Keywords: BSA, MgF2 moderation, experimental validation

Preliminary studies to develop a dosimetric verification of the therapeutic plan for Boron Neutron Capture Therapy using a polymer gel dosimeter

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Boron Neutron Capture Therapy (BNCT), a dual-phase treatment, offers hope to people battling, for example, head and neck cancers and brain tumors. Patients first receive a boron compound attached to a carrier targeting cancer cells, followed by exposure to an epithermal neutron beam.
One important aspect of the therapy is the ability to determine the four main components of the therapeutic dose: gamma dose, fast neutron dose, nitrogen dose, and boron dose. One of the ideas to address this aspect is a head phantom filled with a boron-doped polymer gel dosimeter [1]. The final design of the phantom will allow the verification of the therapeutic plan. Our research is divided into several stages. The first step is to perform computer simulations using Monte Carlo methods, all simulations are performed in the Particle and Heavy Ion Transport code System (PHITS). [2]
As the phantom is to be filled with polymer gel dosimeter, it is an extremely important stage to be familiar with the specifications of this detector. It is believed that ionization with different Linear Energy Transfer (LET) values creates polymer clusters of different sizes, distinguishable using Static Light Scattering and Laser Computed Tomography alike [3]. This leads to the feasibility of creating 3D LET metrics and extraction of relative dose contributions from different components of mixed fields typical for neutron capture reactions.
The next step is to prepare the polymer gel detector readout station. In preliminary studies, a UV-VIS spectrophotometer is used for initial detector readings, and the parameter examined is the absorbance spectrum.
The next stage is to expose the detectors in various sources of ionizing radiation, allowing verification of the detector response. The detector has been irradiated in isotopic gamma-ray sources and neutron radiation fields, among others. Preliminary studies will help determine therapeutic dose components in BNCT based on previous detector responses. The detector will also be used on a research stand at the National Centre for Nuclear Research (NCBJ). At NCBJ, a research stand currently under construction at the MARIA research reactor will allow studies using both thermal and epithermal neutron beams. At the research stand, scientists have planned, a.o. to study the development of BNCT, conduct materials research and test electronics for radiation damage.
In the presentation, we will show the first results of the work carried out and plans for the future.

Acknowledgment
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Keywords: phantom, dosimetry, polymer gel dosimeter

Experimental verification of dose calculation algorithm with a combination of Monte Carlo method and Removal-Diffusion equation for BNCT using a head and neck water phantom

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In Japan, the clinical treatment of BNCT has been implemented for unresectable, locally advanced, and recurrent head and neck carcinomas using an accelerator-based neutron source since June 2020. Considering the increase in the number of patients receiving BNCT, the efficiency of the treatment planning procedure is becoming increasingly important. Therefore, novel and rapid dose calculation algorithms must be developed. We invented the 'MC-RD' calculation method with a combination of a Monte Carlo (MC) method and a method based on the removal-diffusion (RD) theory (RD calculation method). The traditional diffusion theory only takes into account the 'collided' neutrons entering the collision process immediately after occurring at the source. On the other hand, the RD theory takes into account the 'uncollided' neutrons before entering the collision process in addition to the collided neutrons[1)]. In this presentation, we will present the details of our invented MC-RD calculation method and the verification results of the calculation accuracy based on the full-MC calculation result and experimental result in terms of thermal neutron flux distribution inside a head and neck phantom filled with water.
In the MC-RD calculation, the MC and RD calculation methods were used to simulate the moderation and thermalization processes of neutrons, respectively, as follows. First, the energy where the neutron decelerates from the moderation process to the thermalization process was set as 1 eV in this study. The distribution of neutrons terminated below 1 eV in the phantom after being produced from the neutron source was derived using MC calculation with the cutoff function by setting the cutoff energy to 1 eV. Then, the distribution was used as the source for the calculation of uncollided neutron fluxes in the RD calculation. The source for the calculation of collided neutron fluxes was derived from the distribution of uncollided neutron fluxes. Finally, thermal neutron fluxes were derived by summing the fluxes of uncollided and collided neutrons with the energy below 0.5 eV. Here, the RD parameters, such as cross sections and diffusion coefficients, were determined by MC calculations in advance. The MC calculations were conducted using PHITS[2)].
In addition, the measurement of thermal neutron flux was conducted for the experimental verification as follows. Bare and cadmium-covered gold wires were set in the 3D-printed head and neck phantom filled with water[3)]. Then, the phantom was irradiated by the epithermal neutron beam in the Heavy Water Neutron Irradiation Facility of Kyoto University Reactor[4)]. The gamma rays emitted from gold wires were measured using a Germanium detector to derive the activation reaction rates. Thermal neutron fluxes were determined from the reaction rates of gold wires.
The MC-RD calculation accuracy was verified by comparing the results of the MC-RD and MC calculations and experiment for the thermal neutron flux distributions inside the phantom. Here, the MC-RD calculation cannot include neutrons decelerating below 1 eV before reaching the phantom surface. In the experimental verification, the MC-RD calculation result was added by the MC calculation result for the neutrons below 1 eV in the front of the phantom surface.
The MC-RD calculation mostly reproduced the thermal neutron flux distribution derived by the full-MC calculation and experiment. However, there was a discrepancy due to the diffusion approximation and assumption about the angular distribution of neutrons terminated below 1 eV, especially in the region near the surface. In addition, the MC-RD calculation time was reduced by about 87% from the MC calculation for neutron source larger than 1 eV at the downstream surface of collimator.
In conclusion, the MC-RD calculation method is useful for fast evaluation of the neutron flux distribution for BNCT dose calculation, except for the region near the surface.

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Keywords: dose calculation algorithm, Removal-Diffusion theory

Radiobiological concepts and their application in a recently developed Treatment Planning System in BNCT: the application on a glioblastoma in NEMESIS facility. Radiobiological concepts and their application in a recently developed Treatment Planning System in BNCT: the application on a glioblastoma in NEMESIS facility

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A Treatment Planning System (TPS) has been designed for dose-volume estimation of a BNCT treatment from patient's images. The TPS gathers information from patient DICOM images (CT, MRI, and/or PET/CT) and applies geometry and material extraction to the Monte Carlo simulation code MCNP v6.2. A neutron beam, previously modeled from a Monte Carlo code such as MCNP, PHITS or Geant4 can be used as input to the dose engine of the TPS. For the elaboration dose reports, various dose computation models, such as dose-volume histograms and isodose maps, can be used. The TPS helps on the prediction of an optimized BNCT treatment application.
The dependence of the biological damage with the neutron energy is an important aspect that should be included in detail in any tissue damage calculation. Especially in the range of epithermal energies, the dependence of the damage with the beam spectrum can be crucial. However, this fact is not easy to include in the dose estimation, that is why we introduce the concept of Weighted Kerma Factors, an extension of the so-called Kerma Factors that includes the biological effect of each neutron energy. By adding these Weighted Kerma Factors to the MCNP computations, it will be possible to derive the dependence of the damage with the beam straight from the Monte Carlo simulation, cutting down on computation costs and improving damage estimation.
The isoeffective formalism for biological dose calculation as well as the use of the Weighted Kerma Factors has been included in the developed TPS, being capable to predict in detail the outcome of a BNCT treatment on a real patient from its DICOM image and taking into account the influence of the beam spectrum on this damage. The beam corresponding to the Spanish projected BNCT facility (NEMESIS)[1,2] was applied to a glioblastoma case in order to compare with previous results and to search for the optimized conditions for a treatment application.

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An innovative toolkit to simulate neutron capture therapy irradiation and dosimetry.

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Boron Neutron Capture Therapy (BNCT) is an advanced modality in cancer treatment, leveraging the unique interaction between boron-loaded compounds and thermal neutrons. A crucial component in the implementation of BNCT is the Treatment Planning System (TPS), a complex tool designed to facilitate precise and individualized treatment strategies. In this study, we present the development of an open-source TPS tailored for BNCT [1], addressing key functionalities crucial for effective treatment planning. This TPS has been developed within the INFN IT_START project.
Our TPS demonstrates the capability to read Digital Imaging and Communications in Medicine (DICOM) and RTSTRUCT files, allowing seamless integration with existing medical imaging and radiation therapy infrastructure. This interoperability ensures compatibility with various imaging modalities and treatment planning processes.
One notable feature of our TPS is the incorporation of a flexible neutron beam direction selection interface. This functionality contributes to the customization and optimization of treatment plans for enhanced therapeutic outcomes.
Furthermore, the TPS includes robust capabilities for simulation input preparation and output analysis. It streamlines the workflow by facilitating the preparation of inputs for Monte Carlo simulations, a pivotal component in assessing the neutron flux and dose distribution. The TPS seamlessly reads and interprets simulation outputs, providing results with valuable insights into the predicted treatment effects.
A distinguishing aspect of our TPS is the integration of diverse dosimetric models (ex. RBE weighted, iso-effective) allowing for comprehensive evaluation of the irradiation effects. These models incorporate radiobiological parameters, ensuring the correct evaluation of the dose distribution within the targeted tissues. Such versatility enables us to tailor treatment plans based on patient-specific characteristics and tumor geometry.
The emphasis on open-source development is paramount in our approach. By adopting an open-source framework, we advocate for transparency, collaboration, and widespread accessibility in the advancement of BNCT. This not only fosters innovation within the scientific community but also promotes the democratization of advanced treatment planning tools, particularly in resource-limited settings.
In conclusion, the presented open-source BNCT Treatment Planning System wants to promote sharing knowledge within the ISNCT community. Moreover, with its capability to integrate seamlessly into existing clinical workflows, provide flexible neutron beam direction selection, streamline simulation processes, and incorporate diverse dosimetric models, our TPS stands as an asset for BNCT researchers. The commitment to open-source principles underscores our dedication to advancing BNCT research and facilitating global access to innovative treatment planning technologies.

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Keywords: BNCT, TPS, Dosimetry, Isoeffective, CIRT

Measured whole-body dose in accelerator-based BNCT treatment

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Boron Neutron Capture Therapy (BNCT) is biologically targeted radiotherapy where radiation dose is produced with epithermal neutron irradiation that is thermalized in tissue. Thermalized neutrons interact with boron-10 nuclei that have accumulated to tumor cells via infusion of a boron-10 carrier, which causes a high local radiation dose. Neutron beam produces also dose to the healthy tissue through radiative capture of thermalized neutrons that yields mainly 2.2 MeV gamma rays. This property produces whole-body dose that the patient gets from the radiotherapy treatment. For patient safety reasons, whole-body dose of BNCT treatments should be evaluated before starting patient treatments. This evaluation has been previously done in other treatment facilities [1-3].
Commissioning of an accelerator-based BNCT facility is ongoing at Helsinki University Hospital BNCT facility [4]. Our objective was to measure the off-axis dose levels in patient mimicking water phantom. Dose and activation calculations were performed with GEANT4-based Monte Carlo simulation treatment planning system that has been developed for Helsinki BNCT facility and is interfaced through RayStation. The other objective was to compare the calculated results to the measured ones. The statistical uncertainty of the calculations was evaluated by repetition. Our phantom consists of five canisters (height 31 cm, width 19 cm, depth 22 cm) each containing approximately 10 liters of water and the total length being 155 cm. Gamma dose was measured with Exradin thimble chamber M2 ionization chamber with magnesium tip covered with a PMMA cap in six positions outside and between the canisters up to a distance of 130 cm from the beam axis. The measurement points were chosen to represent top of the head, neck, thorax, pelvis, legs and feet. The neutron field was studied by measuring neutron activation with diluted Au and Mn foils taped on the surface of the canisters at approximately equivalent positions. Positioning of the phantom with relation to neutron beam axis was chosen to resemble that of a head-and-neck treatment and irradiations were performed with robotic couch and image guidance.

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Keywords: Accelerator-based BNCT, dosimetry, whole-body dose,

Development of real-time boron-concentration estimation method using the improved gamma-ray telescope system for boron neutron capture therapy

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Introduction

It is important to decide the boron concentrations for tumor and normal parts in the dose estimation for boron neutron capture therapy (BNCT). The on-line and real-time estimation method for the spatial distribution of boron concentration is expected for the advancement in dose estimation. The information about the boron concentration distribution can be obtained using the prompt gamma-ray analysis (PGA) for the 478-keV prompt gamma rays generated due to the nuclear reaction of boron-10 (B-10) with thermal neutrons. The improved gamma-ray telescope system is settled at Heavy Water Neutron Irradiation Facility (HWNIF) of Kyoto University Reactor (KUR) [1-3]. This system is composed of an HPGe semiconductor detector and a collimation system including two lead collimators. The gamma rays through the two collimators can be detected, and the view-field of the telescope can be expanded or reduced by moving the two collimators independently. The experimental verification for the improved telescope system was performed. The experimental data was compared with the simulated data to calculate the specification coefficient.

Materials and Methods

The phantom experiment was performed using the epithermal neutron irradiation mode at KUR-HWNIF. The phantom size was 20 cm × 20 cm × 20 cm. Within the phantom, a 5-cm diameter acrylic hollow sphere was placed as the tumor. Both the phantoms and tumor spheres were filled with different concentrations of boric acid water. The tumor spheres with the B-10 concentration of 70, 100 and 200 ppm were put into a phantom with B-10 concentration of 20 ppm. The irradiation field was set to 12 cm in diameter. The tumor sphere was fixed at the center of the telescope's view field. The 1st and 2nd telescope collimators were set at the bottom of the telescope. The simulation calculation was performed using PHITS (Particle and Heavy Ion Transport cord System) version 3.25 [4]. In order to simplify the simulation process, the irradiation room and the telescope system were separately used as the simulation geometry. The specification coefficient was defined as $\tau = C/C'$, where C and C' were the experimental and simulated data, respectively. Regarding this coefficient, it was necessary to compare the counts of 478 keV prompt gamma rays in the experiments and simulations with the same parameters. Since the input file of the detector in the simulation was made based on the energy distribution of the beam, and the data obtained from the simulation was flux, therefore the specification coefficients also carried the magnitudes. By comparing them with three B-10 concentrations of tumor spheres, the error in the calculation could be reduced.

Results and Discussion

The count rates for 478-keV prompt gamma rays with the different irradiation conditions were obtained from the experimental results. In the case of the 70 ppm tumor sphere, the experimental count rate was 29.6 cps (s^{-1}). On the same condition, the simulated flux was 8.97×10^{-5} $cm^{-2}s^{-1}$, and then the specification coefficient τ was calculated to 3.30×10^{5} $cps/cm^{-2}s^{-1}$. The average of the specification coefficient was calculated to 3.48×10^{5} $cps/cm^{-2}s^{-1}$, for the tumor spheres of 70 ppm, 100 ppm and 200 ppm. From the results of the experimental verification, the effectiveness and usefulness of the improved gamma-ray telescope system were confirmed, and the specification coefficient was obtained. The more precise estimation will be performed for the B-10 concentration, size and position of the tumor sphere, and for the position of two telescope collimators. Moreover, the effective range for the discrimination between tumor and normal parts will be clarified.

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Microdosimetry: a technique for beam quality monitoring in BNCT

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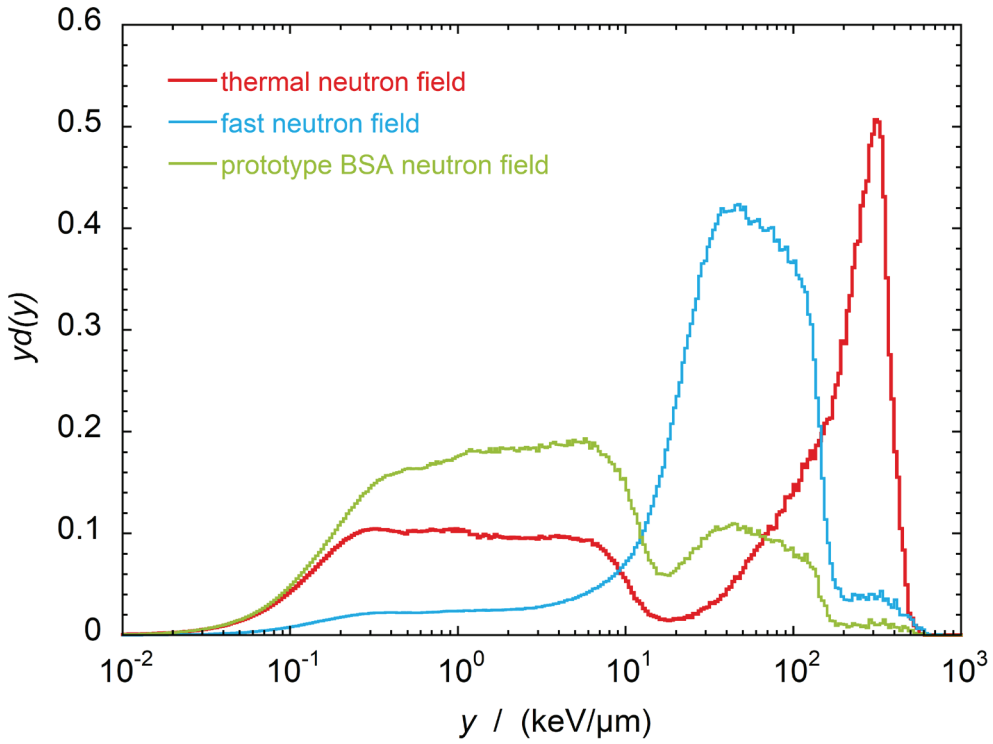

Figure captions: Fig. 1: microdosimetric spectrum measured after a moderator thickness of 27 cm, compared to data for a pure thermal and a pure fast neutron field.

A fast and accurate in-phantom monitoring of beam quality is particularly challenging for BNCT, where the radiation field is composed by several components with widely different biological effectiveness. A suitable experimental tool towards this aim is microdosimetry, i.e. the measurement of stochastic fluctuations of energy imparted by radiation at the micrometre scale [1]. Microdosimetric techniques allow to discriminate the photon, neutron and BNC dose components at different spatial scales [2]. In addition, an estimation of the Relative Biological Effectiveness (RBE) of the radiation field can also be obtained, which could be useful for intercomparisons between different BNCT neutron sources.
Reference measuring devices in microdosimetry are Tissue-Equivalent Proportional Counters (TEPCs), gas detectors working in the proportional regime where both the counting gas and the cathode walls have a chemical composition as similar as possible to that of human tissue.
For BNCT applications, the cathode walls can be doped with ^{10}B to reproduce the clinical situation of boron-loaded cancer cells. Many detectors of this type were built and tested at the Legnaro National Laboratories (LNL) of INFN, to be used for beam quality monitoring for BNCT radiation fields [3,4]. These include pairs of identical counters, one doped with boron and the other one without doping, and TEPCs with replaceable cathode walls, to perform measurements at different boron concentrations [5].
In view of the development of a new BNCT facility in Caserta in the framework of the PNRR-PNC ANTHEM project, one of these detectors was used to characterize accelerator-based prototype neutron sources, producing thermal, epithermal and fast neutron fields. These sources are all based on 5-MeV protons hitting a three-layer beryllium target, as proposed for the final full-scale ANTHEM source. More specifically, microdosimetric measurements were performed at the MUNES thermal neutron source, available at LNL [6], and with a prototype beam shaping assembly (BSA), which integrates many key elements of a clinical setup, such as a moderator, a reflector, a collimator and stray neutron absorbers.
This work presents microdosimetric measurements performed in both neutron fields with an avalanche-confinement TEPC with interchangeable cathode walls. In the pure thermal neutron field produced by the MUNES source, measurements were

taken both with and without boron doping of the detector walls, allowing to quantify the dose fractions due to photons, proton and ion recoils due to neutron interactions, and BNC reactions. In the complex radiation field produced by the clinical BSA prototype, measurements were taken with a 100-ppm boron-loaded cathode after increasing thicknesses of the moderating material, highlighting the attenuation of the fast neutron component and the increase of the low-lineal energy component. As an example of results obtained in this latter case, Fig. 1 shows the microdosimetric spectrum measured after a moderator thickness of 27 cm, compared to those measured in a pure thermal and a pure fast neutron field.
The consistent data set obtained at these two neutron sources shows the potential of microdosimetry for beam quality monitoring in BNCT, to quantify the dose components at the planned treatment depth and providing a first physics-based estimation of their biological effectiveness.

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Keywords: microdosimetry, TEPCs, dose components

Development and validation of γ-ray dose measurement methods combining 6LiF sintered capsule and Mg2SiO4: Tb (TLD-MSO-S) at accelerator-based BNCT system

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The radiation emitted from the beam aperture of the boron neutron capture therapy (BNCT) system includes not only neutrons with a wide energy range but also γ-ray, which causes an undesirable dose for patients. To implement BNCT in clinical practice, evaluating γ-ray dose by measurements is crucial. Current methods of measuring γ-ray dose in BNCT fields vary depending on the facility. There is a need for a measurement method that can be used universally and whose accuracy is guaranteed. A custom-made thermoluminescent dosimeter (TLD) of BeO powder encapsulated in a quartz glass tube (Panasonic, UD-170LS) has been used for γ-ray dose measurement in BNCT fields in Japan. However, it is not currently manufactured and commercially available. Therefore, we investigated a method that combines a commercially available TLD of Mg_2SiO_4:Tb (TOREC, TLD-MSO-S) and ^{6}LiF sintered capsule and validated its usage for γ-ray dose measurement in an accelerator-based (AB) BNCT system.
For TLD calibration, variation in sensitivity among TLD rods and linearity was evaluated using 6 MV X-rays. When measuring γ-ray doses in a neutron field, it is necessary to consider the neutron dose and the perturbation induced by the ^{6}LiF capsule and the TLD holder. We calculated the neutron dose contribution and the correction factor for the perturbation by the ^{6}LiF capsule and TLD holder at 0-10 cm depths in a water phantom using MCNP. The calculated MCNP result was scaled by the measured ^{55}Mn(n,γ) ^{56}Mn reaction rate. Measurements to determine the scaling factor were performed using a PMMA cylindrical phantom and Al-Mn foils in a neutron field produced by the AB-BNCT system nuBeam (Neutron Therapeutics LCC, Danvers, MA, USA). Finally, we validated our γ-ray dose measurement methods by water phantom measurements in the neutron field using nuBeam. Measurements were performed at 0-10 cm depths of the water phantom more than three times at each depth and averaged. The collimators of 14 cm and 11 cm diameters were used. In this study, the neutron irradiation was set to terminate at a proton charge of 3.5 C.
The results of the calibration test confirmed good linearity, and the calibration factor for converting TLD readings to dose was determined to be 1.39 (reading Gy^{-1}). The variation in sensitivity among TLD rods was generally within ±10%, and a correction factor for variation in sensitivity was assigned to each TLD rod. The measured γ-ray dose was obtained from the TLD doses by subtracting the neutron dose and applying the correction factor for the ^{6}LiF capsule and TLD holder. The γ-ray dose was calculated in a water phantom using MCNP. The calculated and measured γ-ray doses agreed within ±7% at all depths.
In conclusion, the usefulness of our method was suggested for γ-ray dose measurement using a combination of Mg_2SiO_4: Tb (TLD-MSO-S) and ^{6}LiF sintered capsule in the neutron irradiation field of an AB-BNCT system.

Keywords: γ-ray, Quality Assurance, thermoluminescent dosimeter

Biological effects of neutron radiation on human melanoma and melanocytes loaded with BPA

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Melanoma is one of the most aggressive and mutated types of skin cancer and is difficult to treat if it metastasizes. Therefore, it is a good candidate to be treated with Boron Neutron Capture Therapy (BNCT) [1]. One of the most promising models for in vitro melanoma studies is spheroids (3D cell culture model). They have many similarities to tumors such as layered structure, microenvironment, growth kinetics, extracellular matrix production, and some gene expression patterns. Hence, spheroids, are increasingly being used to study the efficacy of anticancer therapies and drug delivery systems [2].
We present the results of research on normal skin cells – melanocytes (HEMa-LP) and two melanoma cell lines, derived from primary tumor (FM55p) and metastasis (WM266-4). The 3D (spheroid) and 2D models of growth were utilized for melanoma cell lines and the 2D model for melanocytes. The concentration of ^{10}B taken up by cells during a 4-hour incubation with boronophenylalanine (BPA, 50 µg ^{10}B/ml) was measured using an Inductively Coupled Plasma Mass Spectrometer (ICP-MS). Neutron irradiation experiments of the cells were carried out in the TRIGA Mark II Research Reactor at the L.E.N.A. Applied Nuclear Energy Laboratory of Pavia University, Italy. Cells were divided into two groups: with and without 4-hour incubation with BPA (50 µg ^{10}B/ml). Then, the samples were irradiated with neutrons at a doses of 2 Gy and 6 Gy (only spheroids). Next, 1 h, 24 h, and 48 h after irradiation, the cells were subjected to biological tests. For cells in the 2D and 3D model, these were: a viability test (trypan blue staining) and the DNA strand breaks assay (comet assay [3]). For spheroids, we additionally performed a proliferation test (assessment of Ki67 protein level by flow cytometry) and evaluation of changes in spheroid shape and size (image analysis).
The results show that irradiation of cells containing ^{10}B inhibits their growth in all cell lines tested and reduces the diameter of spheroids of both melanoma cell lines, compared to irradiated cells without ^{10}B and control (not irradiated cells). Cells containing ^{10}B after neutron irradiation show significant DNA damage compared to irradiated cells without ^{10}B (HEMa-LP, FM55p cell lines in 2D model). The WM266-4 cell line in the 2D model shows no difference in the level of DNA damage between cells irradiated after incubation with BPA (^{10}B) or without ^{10}B. However, melanoma cells in the 3D model have higher levels of DNA damage than the corresponding 2D model. Additionally, the Ki67 assay shows a decrease in the Ki67 expression 48 h after irradiation with a dose of 6 Gy (FM55p cell line with ^{10}B). Interestingly, for the WM266-4 cell line, Ki67 protein levels decrease already 1 h after irradiation and decrease in the following hours for spheroids containing boron.
In conclusion, preincubation with BPA containing ^{10}B as a cell-sensitizing agent causes biological effects such as inhibition of cell growth and increase in DNA strand breaks, and their intensity is related to the neutron dose used and the cell type [4]. The observed differences in the level of DNA damage between the 2D and 3D models may be related to changed cell metabolism and structure of spheroids [5].

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Application of segmentation of heterogeneous boron distribution intraROI

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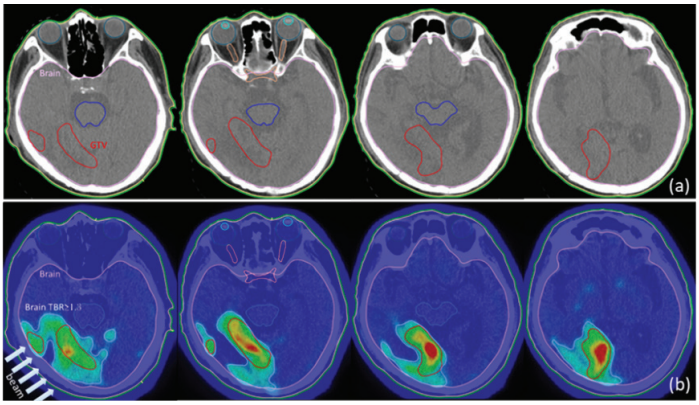

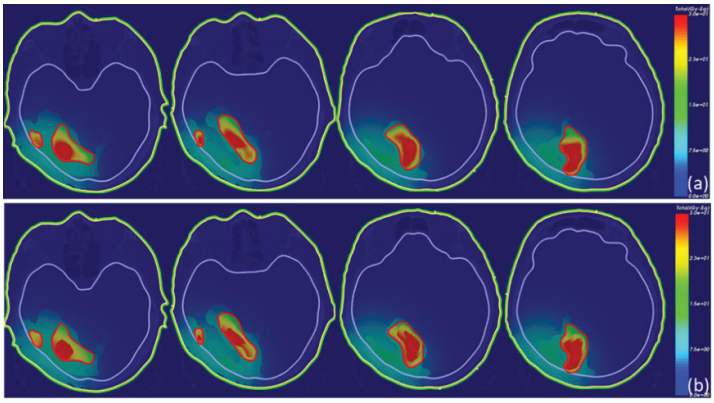

Figure captions:
Fig 1 (a) CT-sim image and RT structure; (b) 18F-BPA PET/CT-sim fusion image
Fig 2 Biologically equivalent dose map (a) hyper-segmentation; (b) hypo-segmentation of heterogeneous boron distribution

Most treatment planning systems of boron neutron capture therapy perform dose calculations based on the assumption of a homogeneous boron distribution intraROI, which leads to dose distortion due to the difference between the target-to-blood ratio (TBR) range measured in positron emission tomography images (PET) and the target delineation in computed tomography simulator images (CT-sim) of the treatment plan. NeuMANTA[1] developed by Neuboron Medical Group uses image fusion technique to obtain and quantify the heterogeneous boron distribution of target region in treatment plans[2]. The heterogeneous boron distribution must be taken into consideration to have an accurate dose estimation. Considering that the image representation is macroscopic, the difference in image resolution between different modalities, and the error in registration and fusion, it is of little significance in dose calculation and clinical evaluation to overly refine the heterogeneous boron distribution. This study utilizes the method of quantifying boron distribution to segment the heterogeneous boron grading range and applies it to dose calculation and assessment of organs at risk and tumors. Take investigator-initiated trial using the NeuPex[3] system for brain tumor case in Xiamen Humanity Hospital (XHH) as an example. The TBR range of brain is 0.02~2.07 and that of tumor is from 0.95 to 3.72, and hyper-segmentation and hypo-segmentation of heterogeneous boron distribution are performed.
The dose results of hyper-segmentation show that the D_{max} of brain is 12.97 Gy-Eq (CBE=1.3, RBE_N=3.2), the D_{mean} is 2.22 Gy-Eq, and the doses above 12 Gy-Eq do not exceed 0.03% of the volume. The Brain D_{max} of hypo-segmentation is 11.79 Gy-Eq, and the D_{mean} is 2.20 Gy-Eq, which differed from the results of hyper-segmentation by 9.1% and 0.9% respectively. The difference of D_{man} and D_{80} of tumor between hyper- and hypo-segmentation of heterogeneous boron distribution do not exceed 1.6%. The tumor D_{min} of the hypo-segmentation is 12.31 Gy-Eq (CBE=3.8, RBE_N=3.2), which is 54.6% higher than the 7.96 Gy-Eq of hyper-segmentation. The volume of the hyper-segmentation of dose lower than 10 Gy-Eq does not exceed 0.08%; the volume of dose lower than 12.31 Gy-Eq, dose does not exceed 0.4%. The dose map of the two are consistent with each other. This demonstrates that heterogeneous boron distribution in hypo-segmentation is sufficient for dose calculation and response assessment.

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3. Advances in Boron Neutron Capture Therapy. 2023, Vienna: INTERNATIONAL ATOMIC ENERGY AGENCY.

Keywords: heterogeneous boron distribution, TPS

The novel i-TED Compton Camera for real-time boron imaging and determination during treatments in Boron Neutron Capture Therapy

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Boron concentration determination and imaging are fundamental for a successful BNCT treatment, both in terms of treatment planning and for dosimetry of the actual dose received by the patient. A Treatment Planning System (TPS) should include reliable inputs of the boron distribution inside the tumor and surrounding organs at risk in order to assess the efficacy of a treatment. Moreover, real-time dosimetry would be key in order to validate the treatment plan and make any possible changes in beam orientation and patient positioning in order to adjust to the prescribed dose in case of variations of the boron distribution during the treatment. The i-TED compton camera, developed at Instituto de Física Corpuscular (IFIC) in Valencia, which has been successfully devised for nuclear physics experiments [1], is now being tested for its use in medical physics applications [2,3]. These detectors are specially well suited for its use as boron imagers by retrieving the 478 keV prompt gamma ray emitted after 96 % of thermal neutron captures in boron, and are intended for real-time boron dosimetry with a high position resolution. To do so, a first step of simulation of the i-TED set-up in conjunction with real patient models is done. This allows an integration of this set of detectors with the TPS recently developed at the University of Granada.
MCNP v6.3 is used as a dose engine for neutron transport and in order to retrieve the gamma rays out of the patient, and Geant4 is used to run the gamma detections in the i-TED camera, in an integrated pipeline connected via MCPL. A later stage of Machine-Learning-based image reconstruction is followed, which allows both imaging and boron quantitative analysis. Results from simulations of the i-TED Compton imaging capabilities for BNCT, using anthropometric phantoms (e.g. ICRP 110 and ICRP 145), as well as real patient models based on DICOM data (glioblastoma cases), will be shown. Treatment plans are based on optimized cases using the BSA and facility designed in the NeMeSis project from University of Granada [4].

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A Spherical Neutron Source Term for Precision Treatment Plan Calculations in Boron Neutron Capture Therapy

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This research is dedicated to the meticulous evaluation and establishment of a neutron source term customized for boron neutron capture therapy (BNCT). Utilizing a comprehensive five-phase methodology, encompassing (1) the design and planning of neutron beam exit measurements, (2) model design and analytical computations employing Monte Carlo programs, (3) experimental measurements and comparisons spanning neutron energy, flux, and angular distribution, (4) analysis, iterative computation, and validation of both experimental and programmatic outcomes, and (5) formulation of treatment plans applicable to MCNP, integrating neutron source terms for prospective and concurrent research initiatives.
The extraction of the neutron angular distribution at the beam exit involves a migration simulation to correlate the angle distribution, spatial distribution, and energy distribution. However, experimental verification of this relationship poses a challenge. The neutron angular distribution of the previous source term THOR y09 source term was indirectly derived through neutron radiography measurements, and the spatial angle distribution was inferred using SAND-II, categorized into three groups. However, our assessment reveals that these three angular distributions fail to effectively restore the true characteristics of the neutron beam. Consequently, this study invested approximately four months in MCNP simulations to obtain detailed angle distributions for each energy group in space. Furthermore, after analyzing the variation of the angle distribution in space, it was observed that the dependence between the angle distribution and the spatial distribution is relatively low, while the dependence between the angle distribution and the energy is highly pronounced. Thus, a spherical source term adopts an angular distribution of 95 groups. Simulation results indicate a low interdependence between the angular distribution and spatial distribution of the BNCT neutron beam. However, the axial angle varies with changes in spatial position and radial distance from the center of the beam, a variation not suitable for adjustment through the angle distribution. Nevertheless, it can be corrected through a three-dimensional spherical surface source to mitigate the axial angle deviation. The THOR SN22 neutron source term, denominated as the Tsing Hua Open-pool Reactor (THOR) BNCT Spherical Neutron Source 2022 (SN22), corrected using a spherical surface, approximates the actual angular distribution changes with space and has been intentionally devised and implemented for treatment plan calculations. Its superiority is substantiated by robust performance in the experimental results. In a gaseous medium, the neutron source term manifests errors of less than 5% within a 10 cm axial distance and 4 cm radial distance, with discrepancies within the primary beam range consistently below 15%. Within PMMA phantoms, radial errors within a 4-cm radius are below 2%, and errors at other spatial positions consistently register at less than 5%. Even when attached to collimators with diverse length/aperture combinations, errors along the central axis of the phantom predominantly remain below 5%, with none exceeding 7%. THOR SN22 emerges as a reliable neutron source term, facilitating precise computations for patient treatment doses and spatial dose assessments, thus providing accurate and reliable simulation results within the domain of neutron therapy.

Keywords: Neutron source term, BNCT

Incidence of the somnolence syndrome after brain tumor treatment with BNCT using a photon isoeffective brain dose model

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Radiation doses administered to organs at risk impose a limit to the treatment. In particular, the brain is a major dose-limiting organ for brain cancer patients undergoing radiotherapy (RT). Adequate estimations of the dose to this organ therefore make it possible to study normal tissue tolerance and assess the potential adverse effects.
The most commonly observed neurological side effect in radiotherapy associated with whole-brain irradiation is somnolence syndrome. Photon RT involves uniform dose distribution in the brain and, then, the volume of irradiated tissue is a determining factor in the occurrence of side effects [1]. The occurrence of somnolence syndrome after BNCT irradiation has been reported [2]. Resulting whole-brain doses are not uniform, and average whole-brain doses or peak doses do not predict the development of somnolence. Therefore, in comparison with uniform photon delivery data, these doses should be used with caution. We propose an approximation to the equivalent uniform dose (EUD) for comparison with photon radiotherapy results. The EUD is the dose that, when distributed uniformly over a given volume, causes the same biological effect as the non-uniform dose delivered [3].
Usually, the "RBE-weighted" dose model was used to translate BNCT doses to photon-equivalent units. For normal tissues, however, this procedure leads to an underestimation of the dose [4]. The concept of photon isoeffective dose was developed in [4] 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 estimated to produce the same biological effect as the combination of the different absorbed doses administered with BNCT.
In this work, we develop 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 irradiations. For this, we propose suitable mathematical expressions to describe the normal tissue complication probability for the reference photon radiation and for BNCT. This gives the first model to obtain the photon dose that produces the same probability of brain toxicity as the BNCT treatment.
We apply the developed model for dose calculation in BNCT treatments of malignant gliomas conducted in Finland [5] and in the clinical trials at Harvard-MIT and BNL (USA) [2]. The calculated doses, compared with adverse reactions expected from conventional radiotherapy, allow us to assess whether the doses are representative of the radiotoxic effects observed in clinical BNCT. As a byproduct of this comparison, we present our construction of the dose-effect curve for somnolence syndrome caused by photon radiotherapy.
The calculation of the EUD involves the entire dose distribution in the brain. Unlike patients from Finland, for whom complete information is available, only mean and maximum doses were reported for the 72 patients treated at Havard-MIT and BNL. We present a model to estimate the EUD in terms of the mean and maximum doses. The model essentially approximates the EUD by a weighted average of these doses, where the weights depend on the number of fields in the treatment. These weights were determined from representative dose-volume histograms for irradiations involving 1, 2 or 3 fields. To validate the model, we compare the exact EUD calculation and the proposed approximation in the Finnish treatments, obtaining differences of less than 3%.
With these, we estimated the EUD in the 72 treatments and, then, constructed the dose-effect curve for somnolence syndrome using maximum likelihood estimation. Comparison of this curve with that obtained from photon radiotherapy strongly suggests that brain doses calculated combining the photon isoeffective dose and EUD models accurately reflect the radiotoxic effects observed in clinical BNCT.

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Keywords: isoeffective dose, brain, somnolence, EUD

Treatment planning of boron neutron capture therapy for superficial head-and-neck cancer

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Treatment planning system THORplan has been used for clinical trial of boron neutron capture therapy (BNCT) since August 2010 under collaboration with Taipei Veterans General Hospital for recurrent head and neck cancer. Recently a study was performed for the effectiveness of using bolus for a superficial oral cancer in improving the tumor dose. The criteria for dose limit of skin is 15 Gy-w, of mucosa is 12 Gy-w. Three cases are calculated. One is without using bolus, one is using bolus on the skin surface of the tumor. To avoid loosen of bolus due to patient movement in the treatment, a 3rd case is tried by putting the bolus at the collimator exit very close to the patient skin. The mass contain of bolus is carbon 77%, hydrogen 14%, silicon 4.2% and oxygen.4.8%. The result shows that by adding a 1cm-thick bolus on the skin surface at the tumor location will greatly improve the mean dose delivered to the tumor by 60%. The tumor locates at 0 - 1.5 cm from the skin surface. The use of bolus shifts the peak of thermal neutron flux to the tumor region. Besides, the peak of thermal neutron flux in the tumor is higher due to more hydrogen contain in bolus (14%) than in muscle (10.2%), which makes more epithermal neutrons slowing down to thermal neutrons. On the other hand, putting the bolus at the collimator exit, instead of putting on the skin, will greatly reduce the fast and epithermal neutron flux entering the skin by ~50%, results in ~40% reduction of thermal neutron flux in the tumor region. Compared to case 1, it only results in slight improvement on the tumor dose. In the 1st and the 3rd cases, the dose limiting tissue is mucosa, while in the 2nd case skin is the dose limiting organ. The treatment time of the three cases are ~ 30 mins, ~35 mins and 40 mins respectively.

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Keywords: boron neutron capture therapy, treatment

Neutron activation in interrupted neutron beams

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Recent advances in the field of boron neutron capture therapy (BNCT) have led to the construction of linear accelerator-based neutron sources on hospital campuses [1]. These neutron sources have almost entirely replaced nuclear reactor-based neutron sources for delivering BNCT treatments. One of the key differences between these neutron sources is that a nuclear reactor does provide an uninterrupted and stable neutron fluence while medical grade linear accelerators feature typically more than a hundred interlocks to ensure stable output conditions of the neutron beam. Consequently, the linear accelerators are in practice likely to feature (relatively short) interruptions triggered by machine interlocks to ensure patient safety. If these interruptions occur during a neutron activation measurement, they will cause a bias to the measurement.
The most important dosimetric quantity in quality and assurance of dose to patient in BNCT treatments is the absolute measurement of the thermal neutrons flux since it is a surrogate for the boron dose in the patient, arising from thermal neutrons being captured by ^{10}B isotopes of a suitable boron carrier agent. The most accurate method in neutron dosimetry for the absolute measurement of the neutron dose is the subjection of diluted foils of a suitable material to neutron activation in the neutron field.
In this study, a simple formalism based on the total number of activated atoms (N_{act}) per monitor unit produced during the beam delivery sequence is derived for dosimetric neutron activation measurements. This formalism is shown to be invariant under multiple beam interruptions without the knowledge of the exact beam interruption and continuation times. It is shown that if the presence of beam breaks is not corrected for, for example by using the reactor era reaction rate formalism, the induced error to the neutron activation measurement is approximately the fraction of pauses compared to the net irradiation time, which may start to dominate the total uncertainty of 2-3% for neutron activation measurements with modern gamma spectrometers. The uncertainty of the N_{act} formalism is shown to be inversely proportional to the half-life of the produced nuclide. For Mn foils, the uncertainty from the formalism is found to be less than 0.5% if the fraction of pauses compared to the net irradiation time is less than 9.0% or 4.5% for a net irradiation time of 0.5 h or 1.0 h, respectively.

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Keywords: Accelerator-based BNCT,neutron activation,neutron dosimetry,quality assurance

Development of a new neutron dosimeter for measurement of ambient dose H* in BNCT irradiation fields

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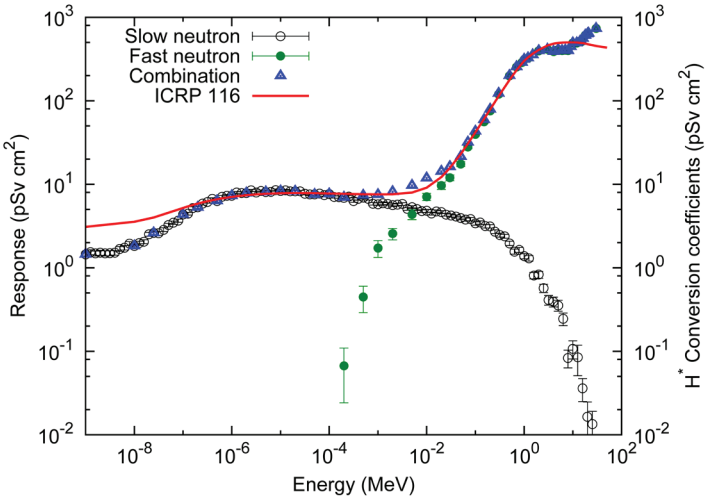

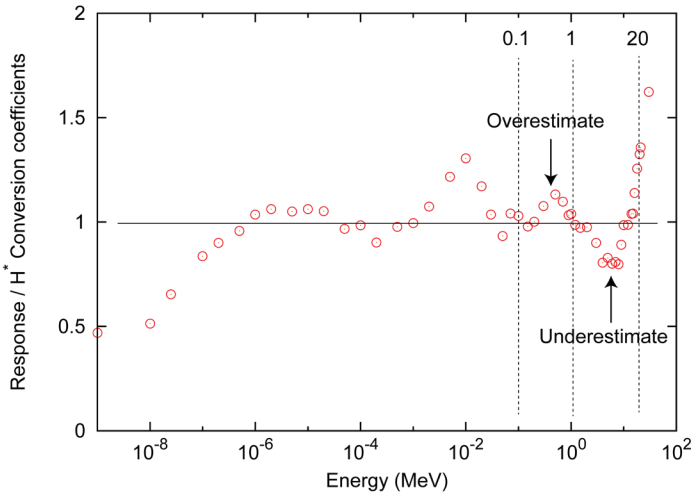

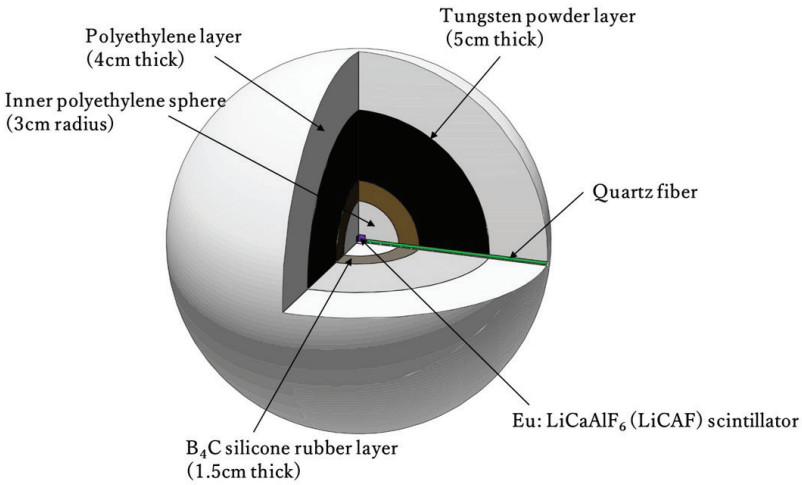

[Introduction] As an indicator of medical devices for proton therapy equipment, the neutron ambient dose as operational quantities outside the irradiation field has been evaluated. It is expected that such evaluation will be required for BNCT treatment devices in the future. However, because of the wide range of neutron energy and intense dose rate in BNCT irradiation fields, existing neutron dosimeters cannot be adapted to measure operational quantities. Additionally, ICRU Report 95 proposed a new definition of operational quantities for external radiation, which replaces the ambient dose equivalent H*(10) with the ambient dose H* to better assess risks [1]. When the recommendations of ICRU 95 are applied in the future, neutron dosimeters for new operational quantities will be required. Therefore, the purpose of this study is to develop a neutron dosimeter that can measure H* suitable for the irradiation field of BNCT.

[Methods] To measure H* accurately over a wide range of neutron energies, we adopted two types of neutron dosimeter. One is sensitive to low energy neutrons from 10^{-10} to 10^{-2} MeV and the other has sensitivity to high energy neutron from 10^{-2} to 28 MeV, the maximum energy of cyclotron-based epithermal neutron sources(C-BENS)[2]. We selected the combination of a small Eu: LiCaAlF$_6$ (LiCAF) scintillator and a quartz fiber as a thermal neutron detector [3]. Polyethylene, B_4C silicone rubber, and tungsten powder layers were installed outside LiCAF as neutron moderators, shields, and generators, respectively. The neutron response functions were obtained by PHITS 3.32 Monte Carlo simulation. The thickness of each layer was optimized by comparing response function with fluence-to-H* conversion coefficients given in ICRP Publication 116[4]. H* was evaluated by using the neutron energy spectrum of 0, 10, 25, 50, 75 cm from the beam aperture center of C-BENS and the neutron response function of the optimized design.
[Results] The optimized design for low energy neutron is a polyethylene sphere of 6cm in diameter. The optimized design for high energy neutron dosimeter has 4 layers, which consist of an inner polyethylene sphere (3cm radius), a 1.5cm thick B_4C silicon rubber,

a 5cm thick tungsten powder, and a 4cm thick outer polyethylene layer in order from the center. The slow and fast neutron response functions, and these combinations were shown in Figure 1. The ratio of the response function to fluence-to-H* conversion coefficients was shown in Figure 2. The ratios were 0.5 and 1.5 in the thermal neutron region and maximum energy. In the other energy regions, the values were within ±0.3, indicating that the measurement error is comparable to that of a commercial neutron survey meter. When H* was evaluated for the C-BENS neutron energy spectrum up to 75 cm, it agreed with the ICRP 116 coefficient within ±5%. The reason for the small difference of 5% in H* is that the majority of the dose is contributed by neutrons from 0.1 MeV to 20 MeV, and the ratios are overestimated from 0.1 MeV to 1 MeV and underestimated from 1 MeV to 20 MeV, which are offset.

[Conclusion] A neutron dosimeter suitable for the BNCT irradiation field was designed for the new operational quantities H*. The optimized neutron response functions were shown to be as accurate as those of commercial neutron dosimeters. Although there is no experimental data at this stage, the prototype will be manufactured and irradiated in accelerator based BNCT irradiation fields in the future.

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Keywords: new operational quantities, accelerator-based neutron source, neutrondosimeter, ambientdose, Monte Carlo simulation

Development of a BNCT dose calculation program COMPASS-GPU based on GPU acceleration and Monte Carlo Method

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Background: Boron Neutron Capture Therapy (BNCT) is an emerging treatment for cancers such as head and neck and brain cancers. An essential part of BNCT is developing a patient-specific treatment plan, which includes accurate dose calculation. Traditionally, this is achieved using the Monte Carlo method, known for its precision but hindered by slow computation speeds on standard computer hardware. Lee et al. employ the multi-group Monte Carlo method to calculate neutron flux. The accuracy of this method is lower than that of the continuous-energy Monte Carlo method. Consequently, Lee et al. emphasize that in the case of a head CT voxel model, the mean absolute percentage errors for neutron flux and absorbed dose are 3.98% and 3.91%, respectively, which is considered unacceptable in radiotherapy.
Methods: This work introduces a novel BNCT dose calculation program, COMPASS-GPU, that enhances the existing Monte Carlo-based COMPASS engine. COMPASS-GPU employ continuous-energy Monte Carlo method to ensure the accuracy of dose calculation. That's why COMPASS-GPU leverages GPU acceleration to significantly boost calculation speeds without compromising accuracy. By integrating GPU-optimized Monte Carlo algorithms, such as event-based Monte Carlo, COMPASS-GPU achieves higher efficiency in dose calculations.
Results: Testing with a head and neck tumor model, COMPASS-GPU displayed the mean absolute percentage errors of 1.28% per voxel dose, aligning closely with MCNP6's statistical error rates (1.52% for MCNP6 vs. 1.26% for COMPASS-GPU). Remarkably, on an RTX4080 GPU, COMPASS-GPU processed millions of voxel grid cases in about 3 minutes, approximately 100 times faster than MCNP6 on a 16-core R9-5950X CPU.
Conclusion: The enhanced speed and maintained accuracy of COMPASS-GPU meet clinical demands and pave the way for its application in large-scale BNCT treatments.

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Keywords: Dose Calculation, Monte Carlo Method, GPU Acceleration, BNCT

Composite detectors as an beneficial tool for dose measurements in BNCT

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Although theoretically the phenomenon of epithermal neutron collisions with the ^{10}B isotope has been studied and described, many questions remain unanswered. Especially in the context of clinical applications, i.e. BNCT, the phenomenon of propagation of secondary particles and quanta (^{2}H and ^{7}Li particles and γ-rays) and their interaction with the human body, both containing boron in cancer and normal tissues, requires further research. It seems that composite detectors can be a very important tool for detailed study of the effects of secondary radiation and its importance for estimating and even measuring the dose absorbed by tissues from various types of ionizing radiation. Phantom experiments on the so-called thin neutron beams will provide key information required by TPS (treatment planning system) for modelling the dose distribution in the patient's body. In turn, composite detectors based on multilayered luminescent materials, enabling the separation of the signals generated by various particles and quanta, are excellent candidates for in vivo dosimeters in the BNCT procedure using the scintillation, TSL or OSL phenomena. The main approach for the creation of these detectors is based on the using significantly different pathway of corpuscular particles with high LET and quanta with low LET in the multilayered luminescent materials. First of all, the thickness of upper luminescent materials can be chosen close to the pathway of the ^{7}Li and α-particles. In second, the bottom part of detector can contain thick enough materials dedicated to the registration of high-energy γ-rays with energy of 478 KeV or γ-quanta with other energy. The main approach to creating these detectors is based on the use of significantly different paths of high-LET corpuscular particles and low-LET quanta in multilayer luminescent materials. First, the thickness of the top luminescent materials can be selected close to the path of the ^{7}Lu and α-particles. Secondly, the lower part of the detector may contain appropriately thick materials intended for recording high-energy γ-rays. In this work, we developed several types of detectors to measure the radiation dose of various nuclear reaction products in BMCT procedure based on all solid-state multilayer epitaxial structures prepared by the liquid-phase epitaxy (LPE) growth method. This type of detector contains first and second single crystalline films (SCF) of light luminescent materials, grown by LPE method, with thicknesses in the 3-5 nm and 12-15 μm range, designed to absorb ^{7}Lu and α-particles, respectively, and a thick substrate prepared from heavy luminescent materials with a thickness in the 0.5-1 mm range used for recording γ-quanta. The luminescent materials for composite detectors can be the tissue equivalent Al_2O_3 sapphire with Ti and Mn activators in the films, and C and Ca,Mg dopants in substrate; the relatively light $Y_3Al_5O_{12}$ garnet (YAG) with Ce and Pr dopants in SCFs and Sc ions in the crystalline substrate, as well as Ce^{3+} doped YAG and $Tb_3Al_5O_{12}$ (TbAG) garnets in SCFs and $Gd_3Al_{2-3}Ga_{3-2}O_{12}$ garnets (GAGG) as the substrate. Appropriate epitaxial structures were grown using LPE methods, and the scintillation, TSL and OSL properties of these composites were examined under selective excitation with α- (^{239}Pu) and β- (^{90}Sr+^{90}Y) particles and γ-quanta (^{137}Cs). The results were compared in terms of selecting the best composition for the direct BNCT procedure in laboratory conditions.

Keywords: Luminescence, detectors, crystals, films, LPE

Measuring 10B Superficial Density with Timepix Quad Detectors

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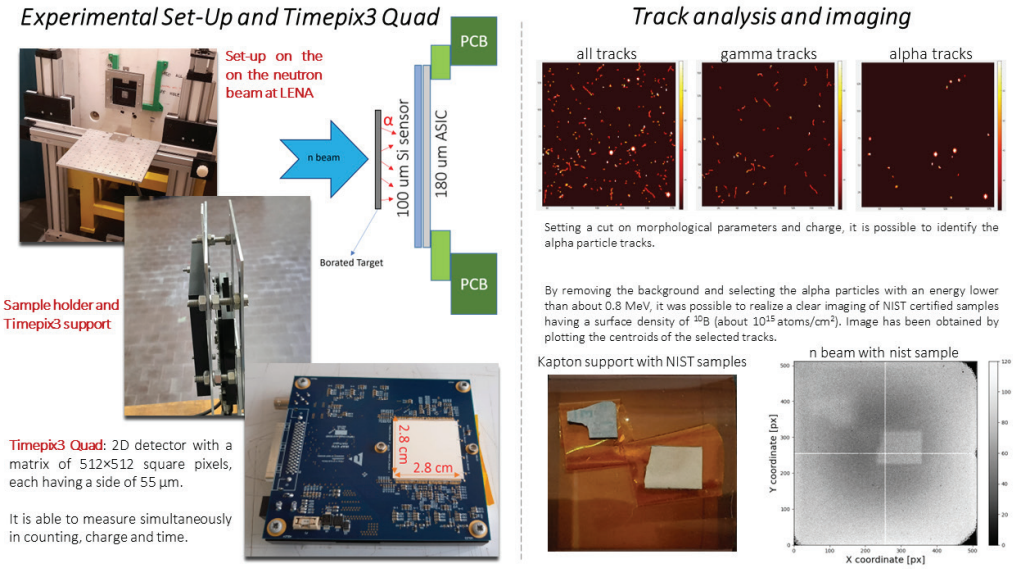

Knowledge of the ^{10}B content in biological samples is of fundamental importance in the field of Boron Neutron Capture Therapy (BNCT). The effectiveness of the treatment is related to the concentration of ^{10}B in the tumor cells and its spatial distribution. Over the years, various methods have been developed to measure these two quantities [1]. The BNCT group in Pavia uses α Spectrometry [2] to measure the concentration and Neutron Autoradiography [3] to image its spatial distribution. The two techniques are applied separately and using different methods and detectors; moreover, autoradiography is laborious and involves the destruction of the analyzed sample; in particular, quantitative analysis by autoradiography requires expensive instrumentation and long reading times. In this work, we propose a new technique based on the use of Timepix quad detectors capable of performing, at the same time, the α Spectrometry required to measure the concentration of ^{10}B and imaging of the spatial distribution of this concentration. The first detector is a 300 µm silicon Timepix1 [4] quad, a pixelated detector covering an area of 28×28 mm^2 with 512×512 square pixels, having a pitch of 55 µm. It can acquire in three different modes respect to the incident particles: counting, charge (deposited energy) or time of arrival. Data are acquired as a sequence of time slices and, for each one, data are integrated (frame-based). In this case, the Timepix1 worked in charge mode with slice times short enough to distinguish the contribution of single particles. The presented results demonstrate a significant increase of sensitivity and spatial resolution of this new measurement technique for the evaluation of ^{10}B content in NIST certified samples with a surface density of 10^{15} atoms/cm^2. As a consequence of these successful results, the detection system has been improved using a 100 µm silicon Timepix3 [5] quad having the same pixel configuration of Timepix1 quad but with a reduction of the background thanks to the removal of the underlying support. In addition, it is also equipped with a new acquisition system with ethernet control [6]. Compared to Timepix1, the Timepix3 can work simultaneously in counting, charge and time, while data are transferred in sequence pixel by pixel without integration (data-driven-based). This allow to acquire without track overlapping , a problem encountered with Timepix1, especially for higher particle fluxes. The use of these high resolution 2D devices allow to exploit also the track analysis to distinguish differ types of particles: in fact the interaction of a single particle produce a signal on a cluster of pixels and the spatial distribution of this cluster depends also on the type of particle. This morphological parameter, together to the measure of particle energy, allow a better identification of the α particles respect to background. First results obtained on NIST certified borated samples will be presented outlining the capability of Timepix3 device to discriminate background, realize more accurate α spectrometry and a simultaneous imaging of the boron concentration.

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Keywords: spectrometry, imaging, boron, alpha, timepix

Towards online detection of boron neutron capture events in biological samples using CMOS image sensors

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The comprehension of ^{10}B localization at the tissue level is crucial for understanding the behavior of boron compounds and determining boron concentration ratios. These ratios are highly relevant for dosimetric calculations and planning BNCT treatments. Therefore, several approaches of neutron autoradiography with Nuclear Track Detectors have been developed and widely used for the qualitative and quantitative analysis of boron concentration in in-vitro and in-vivo biological models from BNCT protocols. The aim of this work is to advance towards the development of a new boron imaging technique using commercial CMOS image sensors. The goal is to detect boron neutron capture (BNC) events in real time, concurrently with the imaging of the biological sample. The strategy involves depositing the tissue section on the sensor, acquiring an image of the histological section, and then capturing images while irradiating the array with a thermal neutron flux. This will allow correlating the activated pixels by BNC events with the region of the tissue from which the charged particles were emitted. Three models of commercial backside illuminated CMOS cameras were assessed to select the most suitable for this specific application: Omnivision OV5647, Sony IMX219, and Sony IMX708. The sensor's active zone was directly exposed to radiation in all the experiments, with the encapsulation and external lenses removed. Firstly, the response to a ^{241}Am α-particle emitting source and a ^{60}Co source was analyzed. Subsequently, experiments were conducted in the neutron imaging and BNCT facilities of the RA-6 reactor at Bariloche Atomic Center, where the sensors were exposed to a thermal neutron beam with a γ-ray contribution. Tests were also carried out by depositing a boron carbide tape enriched in ^{10}B over the sensor's active zone to induce the BNC reaction. Throughout all the experiments, images were acquired to characterize the recorded events. This allowed the discrimination of the signal coming from the BNC products from the background events caused by gamma rays.
The presence of boron in the structural composition of the three models was deducted from the analysis of thermal neutron irradiation measurements. To confirm this finding, a neutron autoradiography study of the sensors was performed to estimate the boron concentration in each model. The detectors were deposited on Nuclear Track Detectors (Lexan polycarbonate) and irradiated with a neutron flux in the thermal column of the RA-3 reactor at the Ezeiza Atomic Center. The analysis of the resulting autoradiographs proved a significant presence of boron in the OV5647 and IMX219 sensors, likely attributable to the use of Boron Phosphosilicate Glass (BPSG) in the manufacturing process of integrated circuits. These findings precluded the possibility of using these detectors for the intended application, as the boron concentrations to be detected are similar to those present in these sensor models. Therefore, the SONY IMX708 was selected as the candidate to continue the development of the technique.
It has been reported that the products of the BNC reaction are the main cause of damage in CMOS image sensors when exposed to thermal neutrons. Therefore, the damage to the device was assessed and characterized based on the source characteristics, flux, dose, and exposure time. Additionally, the recorded events during gamma and alpha particle irradiations were separately characterized. This led to the developing of an algorithm for event classification in the mixed-field irradiation images. Tests are also being conducted to evaluate strategies for depositing tissue sections on the active zone, aiming to ensure close contact between the sample and the sensor without causing damage to the pixels and connectors. This novel technique will not only allow obtaining real-time results but also to enhance understanding of the spatial distribution of boron.

Keywords: boron imaging, detection, CMOS, sensor

Study of the performances of a nnUnet Deep Learning model to automatically segment CT images of Glioblastoma cases to enhance BNCT TPS.

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Artificial Intelligence (AI) is nowadays an extremely interesting tool to tackle many challenges in the medical physics world. Many state-of-the-art Deep Learning (DL) models have been developed and tested to obtain the best possible results in image segmentation and contouring. In the framework of the INFN-CSN5 Young Researchers Grant "AI_MIGHT" and the PNC-PNRR ANTHEM project, we have focused on the application of Deep Learning models in BNCT.
Clinical BNCT improvement and personalisation are main objectives in the ISNCT community. In this frame Artificial Intelligence can aid in the efforts to obtain precise and individualised treatments. Deep Learning is a powerful tool that can be used to automatically segment the ROIs of interest for the therapy plan. The application of DL proved promising to segment large datasets of medical images in short time. This could be helpful in clinics because the medical physicists would optimize the positioning with an automatic segmentation and then the physician would refine the ROIs for the final dosimetry calculation. Moreover, it would be an interesting tool for researchers since it would provide access to big datasets of segmented images useful to test their TPS.
In this work we focus on CT images of Glioblastoma cases obtained from a public images database called The Cancer Imaging Archive. We analysed the database and selected the images that were suitable for the automatic segmentation. We chose to use a publicly accessible Deep Neural network called nnUnet that showed very good performances in segmenting different regions. The database was divided in training and testing sets and the network was trained and tested. The performances of the algorithms and the results of the segmentations of the testing set will be shown.
To further evaluate the performances of the nnUnet segmentation we chose some of the testing cases to simulate BNCT treatment plans, using the IT_STARTS TPS developed by the Pavia group. The treatments were planned to obtain an advantageous dose distribution in the tumour with conservative constraint in the healthy brain. Dosimetry was obtained both using the medical segmentations of the tumour and organs at risks (considered the truth) and the automatic segmentations from the nnUnet. Results of these comparison will be shown and conclusion on the suitability of such approach in different cases will be drawn.

Keywords: Artificial Intelligence, Image Segmentation, TPS,Dose

Commercially available Linacs for neutron production

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BEVATECH GmbH and IAP Frankfurt have more than 30 years of experience in successful developments for cw and pulsed proton and ion linear accelerators, linacs. Since 2006, such linacs have been designed and manufactured in Frankfurt for particle therapy and are in operation globally at numerous therapy centers e.g. HIT, Germany, MedAustron, Astria, CNAO, Italy, Shanghai China. A next generation of injector is already designed within the scope of the HITRI+ project.
Most recently, linacs at 2.2 MeV cw with beam currents up to 30 mA on a Li target are in operation. A 2 MeV proton linac on a Li target is in the running in phase at IAP Frankfurt at present. Efficient proton linacs for other neutron production options are as well established at Bevatech – like producing end energies up to 10 MeV for using Be as target. Reliability and industrial readiness could be shown during the production and commissioning of the Radio Frequency Quadrupole and the first cavities for the MYRRHA project in Belgium. The applied linear accelerator technology offered is mature and widely used in industry, medicine and science, and now available also for the production of neutrons for various demands. The linac offering for BNCT and neutron prodution at BEVATECH aims at the medical doctors and end users of the system. Operating software for the linac controls do seamlessly integrate into the therapy control system offering the full flexibility of the therapy software installation. The linac with its neutron production target can be seen as a black box fulfilling its purpose as a working horse targeted to the demands for boron neutron capture therapy with goals defined by the clinical staff. The footprint of the system ranges from 6 m to 11 m depending on the required maximum energy and duty cycle of the machine.

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Keywords: linac, RFQ, DTL, target, controls

Development of fluoride neutron moderators for accelerator-type BNCT

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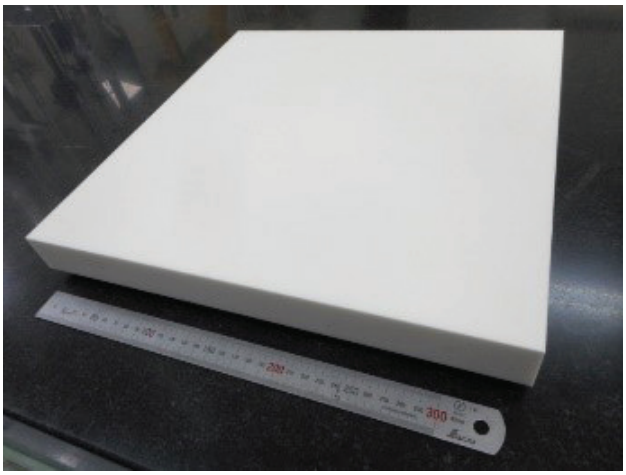

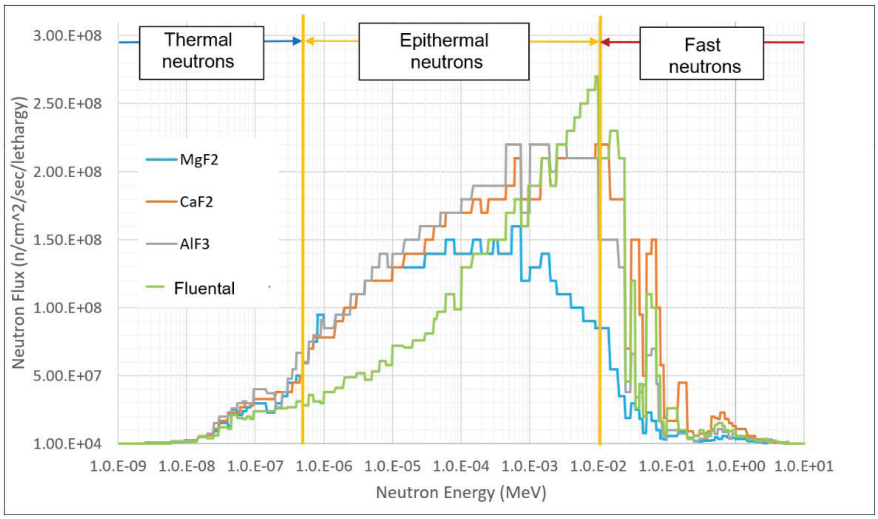

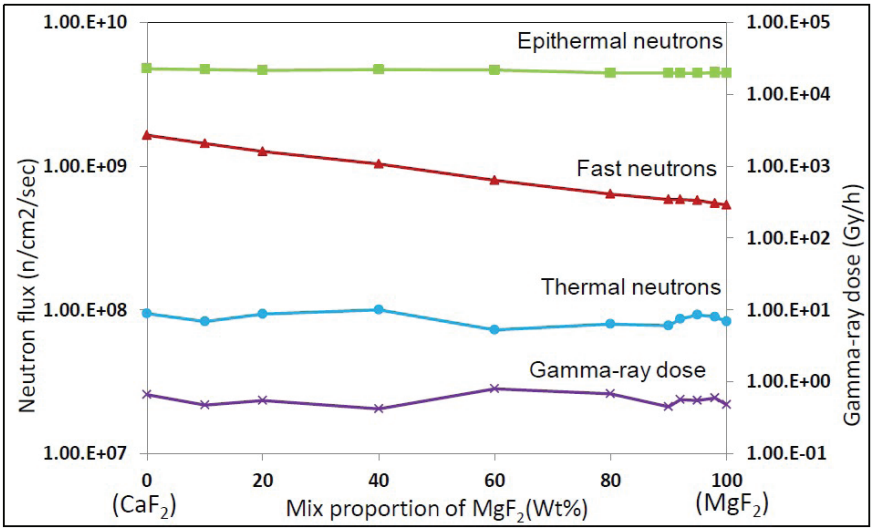

Figure captions:
Fig. 1 Sintered MgF2 tile.
Fig. 2 Energy profiles of neutron flux.
Fig. 3 Compositional dependence of neutron fluxes by MgF2-CaF2 ceramics.

Boron neutron-capture therapy (BNCT) has recently attracted considerable worldwide attention. BNCT projects and related developments are progressing rapidly in many universities and companies. Because an optimal neutron energy is required for BNCT treatment, appropriate neutron moderators are required to adjust the energy of fast neutrons depending on the neutron source. In this study, neutron moderators suitable for accelerator-type BNCT equipment were developed. MgF_2 and CaF_2 were selected as target substances to efficiently moderate fast neutrons from neutron sources to epithermal neutrons. MgF_2 and CaF_2 are usually produced via single crystal growth and pressure-assisted sintering methods; however, it is difficult to produce large, homogeneous bulk materials suitable for BNCT owing to the dimensional limitations of these processes. We successfully produced a dense, highly homogeneous MgF_2 sintered body (> 300 mm square and 50 mm thick), as shown in Figure 1, by processing the starting materials in a unique process, that combined press moulding and a normal sintering process under atmospheric pressure. This process is more cost effective than crystal growth and pressure-assisted processes. The obtained MgF_2 ceramics can be formed into any shape because of their excellent machinability and have already been adopted in selected BNCT projects in which they have been used to generate good epithermal neutron beams for treatment [1]. Figure 2 shows the energy profile simulated for a linear accelerator-type neutron source in the iBNCT at Ibaraki, Japan. A simulation of the beam energy indicated that fast neutrons are effectively moderated and thermal neutrons are reduced by the ceramics produced in this study; this result is in contrast to those obtained for CaF_2, AlF_3, and fluental [3]. However, a cyclotron-type neutron source has a higher neutron energy than that of a linear accelerator-type source, so that a moderator containing CaF_2 is required. The sintering method used in this study enabled the fabrication of a binary bulk body comprising MgF_2 and CaF_2 in any ratio. Homogeneous and dense bulk bodies similar to that of a single composition were obtained by pulverising and mixing the starting materials and adjusting the firing conditions according to the mixing ratio [2, 4]. Figure 3 shows the ratio of the total neutron flux of thermal, epithermal, and fast neutrons, thus facilitating the customised design of the neutron beam energy for each neutron source. Herein, we report the sintering method and the neutron moderation performance of MgF_2 ceramics. References: [1] T. Nakamura, T. Shigeoka, T. Ikeda and H. Kumada, EP 2 865 658. [2] T. Nakamura, T. Ikeda, T. Shigeoka and H. Kumada, EP 3 000 796. [3] H. Kumada, K. Takada, S. Tanaka, Y. Matsumoto, F. Naito, T. Kurihara, T. Sugimura, M. Sato, A. Matsumura, H. Sakurai and T. Sakae, 2020, Evaluation of the characteristics of the neutron beam of a linac-based neutron source for boron neutron capture therapy, Appl. Radiat. Isot. 165, 109246.

Keywords: moderator, MgF2, CaF2, ceramiks,

Development of LiF based ceramics for shielding neutron beam in BNCT

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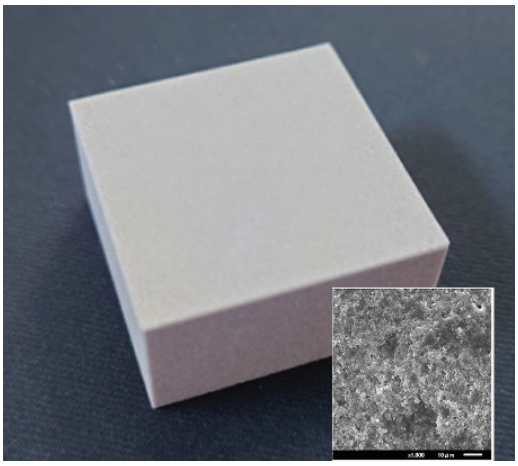

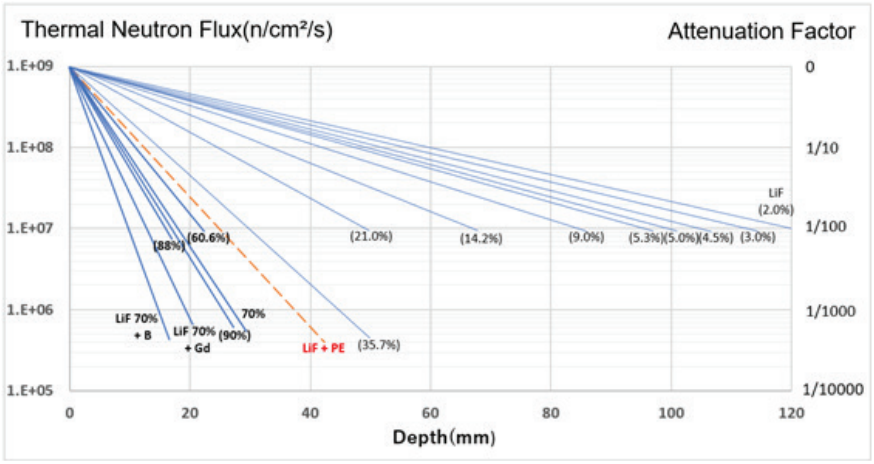

Figure captions:
Fig. 1 Photograph and SEM image of the LiF ceramic tile.
Fig. 2 Simulated depth profile of thermal neutron flux.
Fig. 3 Photograph of the ceramic beads (~3 mm) produced by a grinding process.

Fluoride ceramics that shield neutron beams have been developed for use in Boron Neutron Capture Therapy (BNCT) facilities. LiF, in the form of a composite kneaded with resin materials such as polyethylene (PE), is an effective material for shielding against thermal neutron beams. However, the size of LiF bulk body [1] is limited to small products owing to technical difficulties, although it has a better shielding ability and environmental stability as compared with the composite. We successfully used a normal sintering process [2] to prepare ceramic tiles, up to several tens of centimetres square and approximately five centimetres thick, that were primarily composed of LiF. A relative density above 95 % was accomplished by sintering at the appropriate temperature, as shown in the photograph and SEM image presented in Figure 1. The tile was homogeneous within ±0.1% in terms of its relative density and exhibited good machinability and mechanical strength; these properties ensure its suitability for design of the neutron beam. Therefore, we believe that the tile can be used to shield leaked thermal neutrons around collimators and patients in BNCT facilities. Moreover, we prepared sintered bodies of LiF-based fluorides comprising multiple components that can be used as shields against various neutron sources; the components include moderating materials such as MgF_2 and CaF_2 or shielding elements such as boron and gadolinium. The tile maintains a high relative density (above 95 %) and homogeneity in any multicomponent sintered body. Neutron beam simulations were performed on the tiles using a direct neutron beam from a linear-accelerator-type neutron source [3]. The sintered tiles of the ternary and quaternary systems exhibited a higher shielding performance against thermal neutron beams than that of the currently used LiF-polyethylene composite, as shown in Figure 2. Furthermore, multilayer structures comprising several types of LiF-based fluorides and PE have been designed to accomplish a higher shielding performance. Thermal and fast neutron beams were attenuated more effectively in the multilayered structure than in the single-layer tile. On the other hand, leakage of neutron beam causes activation of an accelerator itself, peripheral devices and the occurrence of adverse events on patients. Based on the simulation of a multilayered structure, we designed

a shielding jig comprising a multilayered structure for the treatment of brain tumours. Additionally, we produced spherical LiF ceramic particles (ceramic beads a few millimetres in size), as shown in Figure 3, for packing into jigs to create a shape variable.

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Keywords: Shielding materials, LiF, ceramics, tile

Comparison of the different Accelerator Based-BNCT facilities worldwide and an update of the Buenos Aires project

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Accelerator-Based BNCT (AB-BNCT) is currently the mainstream option for this unique binary cancer treatment modality. Presently, there are a number of different facilities for AB-BNCT worldwide, some already working and even treating patients and some under development and construction. They range from high-energy 30 MeV cyclotrons (using the ^{9}Be(p,n) reaction), medium-energy RFQ-DTL accelerators (at 8 and 10 MeV using likewise the ^{9}Be(p,n) reaction), low-energy electrostatic, both Tandem and single-ended, and RFQ machines (working on ^{7}Li(p,n) at about 2.5 MeV), to a very low-energy single-ended electrostatic quadrupole accelerator, ESQ (working on ^{9}Be(d,n) or ^{13}C(d,n) at 1.45 MeV). The use of these exothermal deuteron-induced reactions allows us to tackle the task with the smallest energy machine. We shall describe this last accelerator, its ancillary systems and the associated facility which is being developed and constructed at the National Atomic Energy Commission of Argentina. The high voltage generating system was proposed[1] in 2007 and is being used in other machines too[2]. Our machine is designed to work in air to avoid an enclosing tank and the use of a potentially hazardous insulating gas, and for easy maintenance. The accelerator tubes have alternating polarity electrostatic quadrupoles inside, generating strong transverse fields to cleanly guide the beam through the accelerator. Presently the beam current is only limited by the yield of the negative ion source which delivers 15 mA. One of the important aspects to be discussed about these facilities, relevant for their long term sustainability, is the production of radioactivity[3], which should be kept at a minimum according to the ALARA (As Low As Reasonably Achievable; important in an in-hospital facility) criterium, both at the neutron production target, by the primary beam, and the Beam Shaping Assembly (BSA), by the induced neutrons. In a 30 day period with an operation schedule of 8 hours a day the ^{7}Li(p,n) at 2.3 MeV option produces 2.1 TBq of ^{7}Be (30mA), the Be(p,n) option at 8 MeV only produces prompt radiation while at 30 MeV (1mA) other reaction channels are open which produce 0.39 TBq of ^{7}Be and 4.2 GBq of ^{3}H. The ^{13}C(d,t) reaction produces 0.78 GBq of ^{3}H. We have shown[3] that among the systems proposed our solution is the one with the lowest overall activation (target + BSA).
Our system works with low energy deuteron beams and the best option is the ^{13}C target. Coupled to an AlF_3 BSA (which undergoes no activation), a 30 mA deuteron beam can deliver a good quality BNCT treatment for a deep seated brain tumor in one hour (with a maximum tumor dose of 58 Gy-Eq while respecting the maximum tolerable dose at skin and healthy brain, corresponding to 52 ppm of ^{10}B and a tumor to normal brain concentration ratio of 3.5). The graphite target shows excellent properties concerning radiation and hydrogen damage induced by the intense beam. We have chosen a 30 micrometer thick target where the beam stops completely inside the carbon material. The neutron spectrum produced by a 1.45 MeV deuteron beam for such a target has about 70% of the total yield in the region less than 1 MeV. We estimate that this target can stand a power density of about 1 kW/cm2, giving a 7x7 cm^2 area within which the beam has to be uniformly distributed. We have developed a magnetic beam wobbler for that purpose. A half size 0.72 MV machine is already developed. It is a modular machine, each module being of 0.24 MV. A one module machine was transferred to KIRAMS-Korea in 2022. Finally, we report on the construction of a new laboratory and future centre for BNCT.

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Keywords: AB-BNCT, Electrostatic Quadrupole Accelerator, 13C(d,n)

Neutron Beam System for Accelerator BNCT in China: Status and Performance

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An accelerator-based neutron beam system (NBS) has been built by TAE Life Sciences at Xiamen Humanity Hospital in Xiamen, China as a component of Neuboron MedTech's NeuPex™ boron neutron capture therapy (BNCT) system.
The electrostatic tandem accelerator generates a proton beam with adjustable proton energies in the range of 1.8 – 2.35 MeV with currents up to 10mA. Neutrons are generated by the ^{7}Li(p,n)^{7}Be nuclear reaction of the proton beam with a solid thin lithium target. This design makes it possible to reduce the dose from accompanying gamma rays by ~2 times compared to a thick target. These beam parameters, in combination with the NeuPex beam shaping assembly, have provided treatment times for single-fraction BNCT treatments ranging from 30 to 45 minutes. Life expectancy of the lithium target assemblies exceeds 200 mAh with a decrease in neutron yield of less than 10%. Target neutron yield constancy is modeled with neutron and photon detectors, while the buildup of target activity serves as a surrogate for cumulative target lifetime. Replacement target assemblies are supplied by TAE Life Sciences.
The NBS system is configured to deliver the beam to three treatment rooms. At present, beam delivery to only one treatment room has been fully commissioned. Overall energy efficiency of NBS is above 40%, with the tandem accelerator efficiency of 73%.
As of May 2023, 14 patients have been treated by the Xiamen Humanity Hospital as a part of Investigator Initiated Trials. The total operating time of the NBS, mostly dedicated to regulatory and technical tests, has exceeded 2600 mAh to date. In the present single treatment room configuration, the NBS supports treatment of up to 6 patients per day, up to 1,400 per year. This is based on the use of boronophenylalanine, or BPA, for treatments.
The presentation provides an overview of the design and the achieved performance characteristics of the NBS.

Keywords: tandem accelerator, lithium target, protons

A GPU-accelerated Monte Carlo code for Hadron Treatment Planning System

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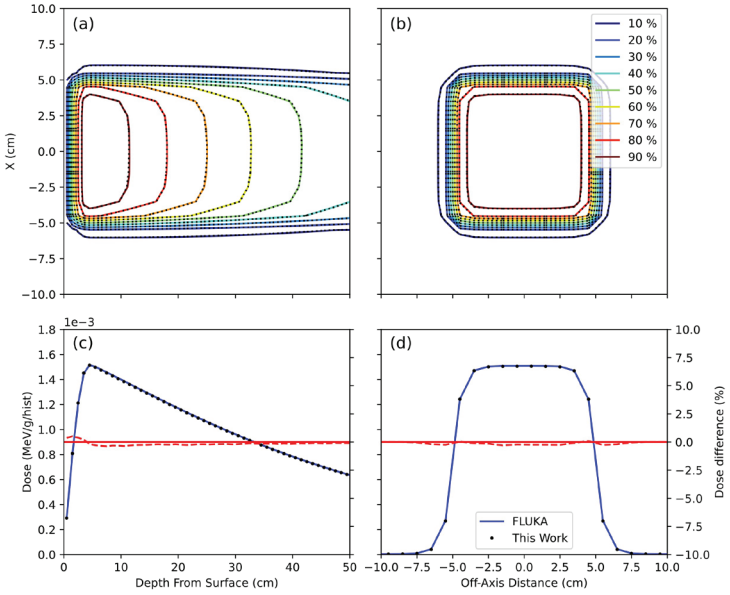

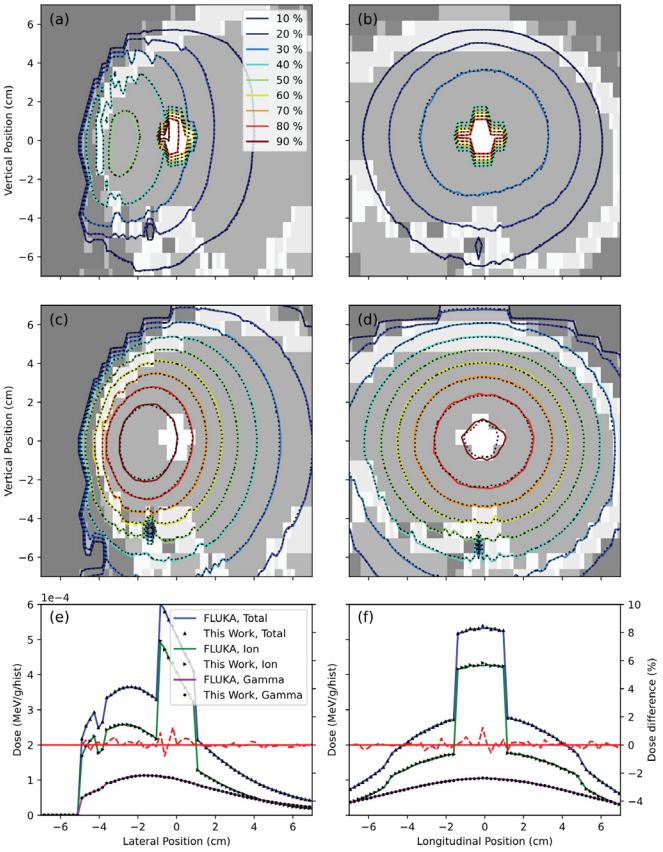

Figure captions:
Figure 1. Calculation results of water phantom with 10 MeV photon.
Figure 2. Comparison results of reference phantom BNCT case.

Background and aims

Hadron therapy is one of next generation modalities for incurable cancer treatment. Implementing these treatment modalities involves an operating software system, a radiation treatment planning system (TPS), encompassing contouring, planning optimization and dose calculation. These procedures require a computing power to ensure guaranteed accuracy within a limited time and the expertise of physician and dosimetrist. To address the first issue, several codes attempting to accelerate Monte Carlo (MC) algorithm using GPUs have been developed in proton and X-ray therapy [1][2]. However, a GPU MC code which can simulate photon and neutron simultaneously has not been developed yet. Further, until recent, there is no TPS commercially dedicated to heavy ions and neutron treatments. Hence, Radiation Transport Monte Carlo (RT^2) code accelerated by GPU Ray-Tracing cores is developed as a high-performance dose engine for BNCT TPS.

Material and Methods

Nvidia OptiX, an application framework for Ray-Tracing (RT) hardware acceleration was employed for tracking radiation particles [3]. To resolve the branch divergence caused by particle type and interaction branches, all transports and interactions are divided into individual kernels. By this approach, calculation and memory access patterns are vectorized. At this moment, RT^2 can simulate neutron, photon, electron and positron simultaneously. The PRESTA-II condensed-history algorithm of EGSnrc code system was applied for electron transport [4]. The ENDF.VII/0 neutron cross-section data were preprocessed by the NJOY21 code system [5]. Neutron transport kernel was developed by an in-house code based on a group-wised transport algorithm. A water phantom and a brain model with the ICRP reference phantom were simulated by FLUKA and RT^2. For the fair comparison, neutron groups of FLUKA were adopted to ours. The FLUKA code was computed on Intel Core i9-10900k and RT^2 was computed on Nvidia RTX 4090. In FLUKA calculations, all available 20 threads of CPUs were used. The 10 MeV mono-energy photon beam was simulated in a water phantom. 5×10^9 photon histories were simulated in both codes. The circular neutron beam that obtained from simulating a beam shaping assembly was simulated in the reference phantom. 1×10^{10} neutron histories were simulated.

Results

The results from photon simulations are presented in Figure 1. In (a) and (b), The iso-dose curve of FLUKA calculation results (colored solid lines) and this work (black symbols) are shown in XY and XZ plane respectively. The red dotted line indicates dose difference between both codes. photon calculation results showed dose differences less than 1% for every point on beam axis and lateral. The computing time of FLUKA calculation was 61850 seconds, while our code was 439 seconds. The

acceleration factor, defined as the ratio of the computing time of our code to that of FLUKA was 140.9. In neutron simulations, the white region inside of the brain indicates designated tumor. 45-ppm and 15-ppm boron-10 were applied in designated tumor and other tissues, respectively. The comparison results are presented in Figure 2. The ion-dose and gamma dose in frontal and sagittal plane are plotted in (a) and (b), and (c) and (d), respectively. The dose difference was less than 1% for all positions along the beam axis and lateral axis in this case. The computing time of FLUKA calculation was 55000 seconds, while our code was 854 seconds. The acceleration factor was 64.4.

Conclusions

The RT^2 GPU Monte Carlo code was successfully developed. With the comparable calculation accuracy, its acceleration factor over the FLUKA calculation was 140.9 and 64.4 in photon and neutron, respectively. Such a superior performance can realize the inverse optimization, and thus enables us to develop an AI-driven & MC-based TPS for hadron therapy.

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[5] R. E. Macfarlane, et al. "The NJOY Nuclear Data Processing System, Version 2012," 2012. Keywords: Treatment Planning System,GPU,Monte Carlo

Performance evaluation of the neutron monitoring system at Xiamen Humanity Hospital-Neuboron BNCT Center

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The Xiamen Humanity Hospital-Neuboron BNCT Center (XHH BNCT Center) has recently celebrated the successful completion of its construction, featuring the installation of the advanced NeuPex BNCT system, a hallmark development by Neuboron Medical Group. This state-of-the-art system operates at a proton beam energy of 2.35 MeV and a beam current of 10 mA. Since the 9th October 2022, clinical studies leveraging this technology have been underway, demonstrating both positive outcomes and significant promise.
A key component of the NeuPex system is its neutron monitoring system, which plays a pivotal role in determining the treatment dose administered to patients. Following its installation, the system underwent a comprehensive performance evaluation, encompassing tests for repeatability, dose linearity (termed Linearity-1), dose rate linearity (Linearity-2), and consistent daily and weekly operational stability.
The neutron monitoring system consists of a meticulously assembled array of three BF3 detectors, three compact nuclear instrument modules, a high voltage monitoring device, and a sophisticated data acquisition system. These detectors are strategically positioned within the beam shaping assembly, maintaining an equidistant relationship from the central axis of the beam and strategically placed relative to the beam exit and the central axis. This design ensures that patient presence at the beam exit during therapy does not compromise the accuracy of neutron measurements. Moreover, this arrangement facilitates multi-point monitoring of neutron intensity distribution across the system.
For performance verification, a standalone BF3 detector and an array of activation detectors were employed. To mitigate the effects of dead time on detection efficiency, the count rate of the BF3 detector was reduced by covering it with cadmium and placing it within a 300 × 300 × 300 mm3 PMMA phantom, situated near the beam exit for measurement accuracy. Additionally, a laser positioning system was utilized pre-measurement to align the phantom's central axis with the beam's central axis. The system's performance metrics, including Linearity-1, repeatability, daily and weekly stability, were evaluated under the specified conditions of 2.35 MeV proton energy and 10 mA current. Linearity-2 was assessed with a variable beam current ranging from 1 to 10 mA at the same proton energy. These metrics were validated by comparing the cumulative neutron counts at the beam exit phantom against those in the three channels of the neutron monitoring system. For long-term stability assessment, the activation detector, covered with cadmium, was placed at the beam exit's center, and the reaction rate per count of the neutron monitoring system was analyzed.
The results demonstrated that the Linearity-1, repeatability, daily stability, weekly stability, and long-term stability of the neutron monitoring system were maintained within a 2% variation range, while Linearity-2 was less than 5%. These findings affirm the reliability and precision of the neutron monitoring system, thus endorsing its suitability for clinical research applications in conjunction with the NeuPex system. Comprehensive details and the methodology of these measurements will be elaborated in the forthcoming complete report and presentation.

Keywords: neutron monitoring system, on-line monitoring,BNCT,BF3counter

Artificial Intelligence acceleration of BNCT dose calculations

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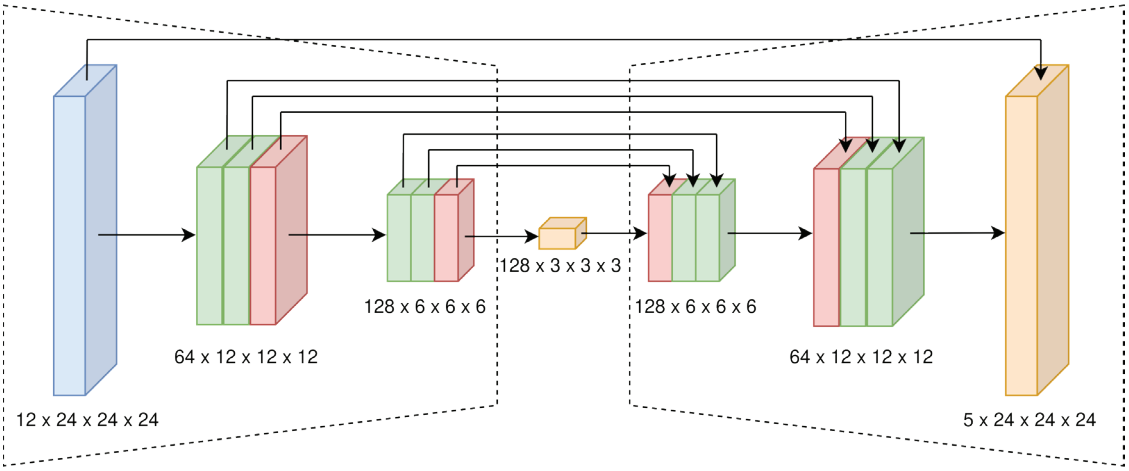

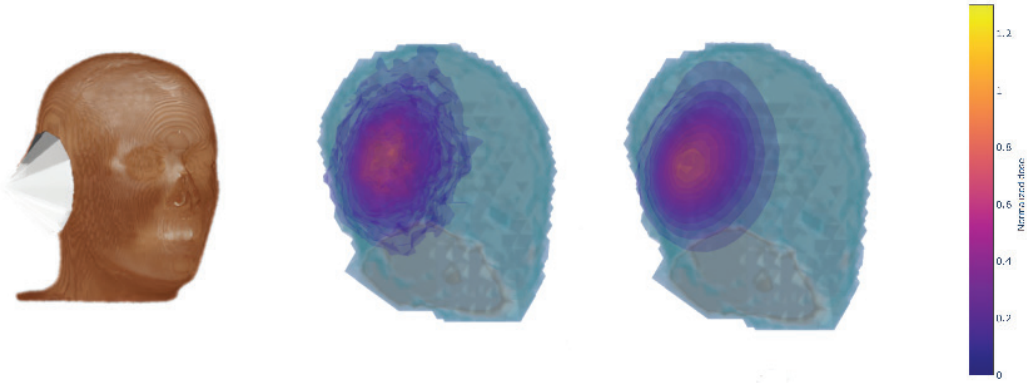

Figure captions:
Fig. 1 – Neural network structure.
Fig. 2 – CT scan of a patient and beam position, 10^4 histories Boron dose simulation and neural network Boron dose estimation (normalized to [0,1] scale).

In the context of Boron Neutron Capture Therapy (BNCT), the impact of the neutron beam employed for patient irradiation extends beyond the neutron capture reaction with the ^{10}B isotope associated with tumor cells. Various interactions involving neutrons or secondary photons with other elements could potentially affect healthy tissues. Hence, meticulous treatment planning is of paramount importance, ensuring that a given neutron beam configuration optimizes the probability of tumor control while minimizing adverse effects on healthy tissues. This optimization is achieved through the calculation of dose maps over tumor and healthy tissues. Traditionally, these dose maps are estimated using neutron transport simulations based on Monte Carlo methods, which, while accurate, entail a substantial computational cost and demand high computational power and long simulation times for convergence and low statistical errors [1]. This complexity poses challenges for comprehensive studies on optimal treatment configurations for individual patients and may impede the widespread adoption of this therapy in medical centers aiming to treat multiple patients daily.
This study introduces a novel approach leveraging a neural network model designed to expedite the convergence of Monte Carlo simulations. The primary objective is to shift the time-intensive aspect of simulations to the training of the neural network, a process performed only a limited number of times. The proposed model is built upon a variant of the U-Net architecture, as illustrated in Figure 1.
The input data comprises the CT scan of a patient, divided in 4 channels corresponding to the different materials present: air, bone, healthy tissue and tumor, along with 10^4 histories simulations of various dose components (boron dose and dose due

to neutrons and photons in different tissues), as well as the error maps for each dose component. Given the relatively low number of histories, these simulations are susceptible to statistical noise due to the algorithm's incomplete convergence. The neural network is trained to predict 10^8 histories simulations (where convergence is achieved) for these dose components, which are then used to compute the final dose map. The L1 norm between the neural network estimations and noise-free simulations obtained through the traditional Monte Carlo approach serves as the cost function for parameter tuning. Figure 2 depicts examples of a patient's CT scan, a statistical noise-corrupted Boron dose component simulated with low statistics, and a noise-free Boron dose component inferred by IA, respectively. Boron dose was used as an example of one of the dose components inferred by the neural network for the sake of visual clarity.

The proposed system underwent training using 80 different beam positions across 200 different patients from the Cancer Image Archive [2], resulting in a total of 16000 training instances. For testing, an additional 2000 instances, corresponding to 25 patients, were employed. Importantly, none of the patient data from the testing set was used during the training phase, ensuring the model's generalization to unseen data. Simulations were made using MCNP6.1 [3] and patients were modeled as 24x24x24 voxel arrays, where each voxel has sides of 1 cm.

Across the testing set, 96.9% of the voxels in the 3D dose maps estimated by the proposed system exhibited absolute differences of less than 5% of the maximum dose calculated in dose maps based on 10^8 histories Monte Carlo simulations. For reference, only 61.4% of the voxels of the 10^4 histories dose maps fulfilled the same requirement. Furthermore, the proposed method achieved convergence with 10^4 less histories than the conventional approach, as inference time of the neural network is neglectable. This highlights its promise as a fast and reliable approach for designing treatment plans within the context of BNCT.

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Keywords: IA, dose estimation, treatment plan

Examination of neutron beam properties to reach deep-seated cancer on BNCT

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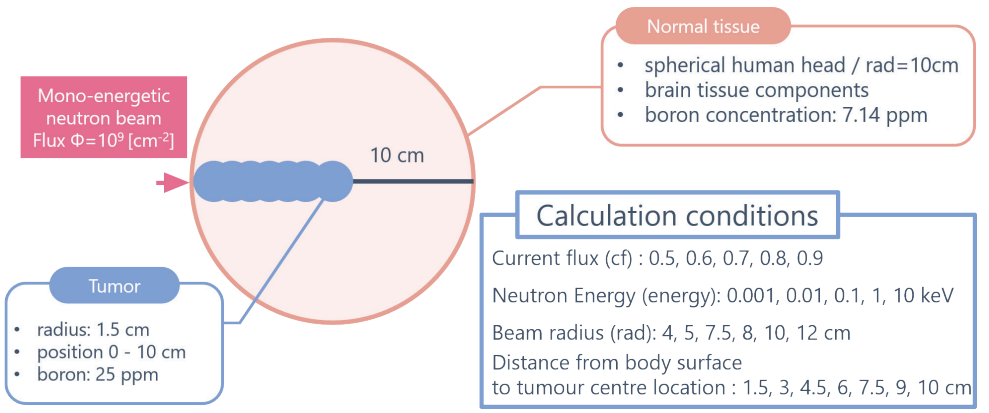

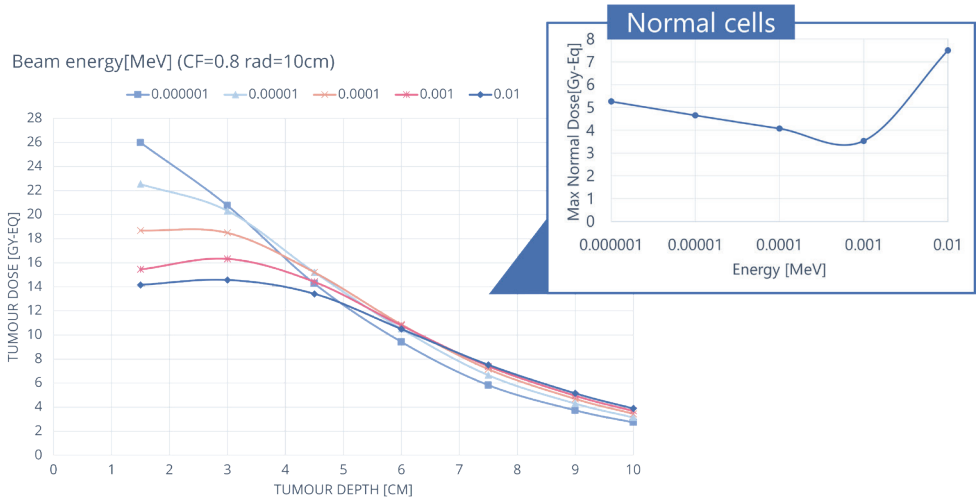

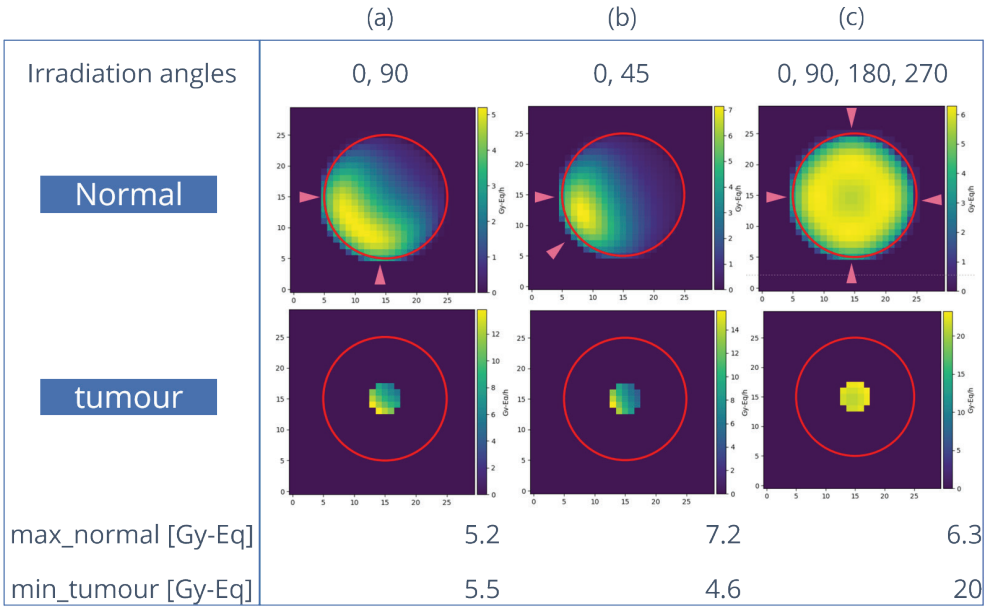

Figure captions:
1. Simulation conditions with spherical human head model.
2. Graph of tumour depth per dose by changing beam energy with that in normal cells. 3. Results of multiple-irradiation trials

Introduction
Although technology has developed and cancer is on verge of being curable, treatment outcomes for deep-seated cancer is sluggish. For example, pancreatic cancer is difficult to endoscopy and inoperable after detection, because it is located behind stomach and spread immediately. Boron neutron capture therapy (BNCT) can have the key to treat them. For expanding treatment lengths of BNCT, previous challenges were carried combination with craniotomy and treatment energy of neutron source was increased. However, its limitation has been still up to about 5 cm. In this study, we looked back at fundamental neutron properties with monoenergetic beam and investigated the possibilities of neutron reach in deeper area for BNCT, considering three elements and multiple irradiations.
Methods

First, three physical properties of the neutron beam, (1) beam radius, (2) energy, and (3) current flux ratio were investigated with varying parameters to study their trends and effects on normal and tumour dose. The current flux ratio is the net incident direction of the neutron and is now defined as over 0.7 for BNCT treatment. [1] Simulations with a spherical model simulating the human head were carried out by changing beam properties and tumour locations as shown in Fig.1. The beam was defined as a monoenergetic beam, and it was simulated to be irradiated directly at the human head. Boron concentration was set as 3.5 in the ratio of tumour cells to normal. The irradiation time was set as 1 hour.

Results and Discussion
In the cases of current flux ratio and beam radius, the larger values corresponded to the more improvements of tumour and normal irradiation dose. Beam energy that maximise tumour dose varied depending on the location of tumour. In Fig.2, at the surface, higher tumour dose was obtained by lower energy and as the tumour location went deeper, higher energy got higher tumour dose in all energy ranges. The attenuation of neutron beam was decreased in the tumour depth of over 6 cm. In the result, the energy that maximises tumour dose depends on tumour depth. However, one direction irradiation was limited up to 4 cm, which achieved 20 Gy-Eq, that is the dose necessary for BNCT treatment. Multiple irradiations system was constructed by using affine rotation and considered to reach deeper area. In the case of two-angle irradiation for a tumour located in the centre of the head, the maximum normal dose was increased more than the minimum tumour dose by irradiation at closer angles as shown Fig3 (a) and (b). In the case of tumour located in 10 cm depth from the surface, irradiations with four angles, at each 90 degrees to each other performed treatable dose score in normal and tumour cells.
It was found that energy values varied depending on tumour location, and 1 keV was found to be the most appropriate energy in terms of both normal and tumour cell dose in deeper area, as opposed to the current BNCT irradiation protocol of 10 keV. The current flux ratio and beam radius increased linearly with increasing values, and further investigation is required with improved upper limits and current flux ratios for setting values in real situation. The next step is the design of the optimal beam spectrum and its simulation studies considering three elements, particularly the neutron energy. In the aspect of multiple irradiations, it could be helpful to improve treatment score in deeper area on BNCT. we also are now preparing experimental validation of this system. In the future, trade-offs between the duration of irradiation and the number of units irradiated should be considered, as well as the burden on the patient.

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Keywords: BNCT, deep-seated cancer, neutron beam,multiple-irradiation

MODELLING OF DIFFERENT CONFIGURATIONS OF BEAM FORMING ASSEMBLY FOR WWR-K REACTOR BY MONTE CARLO METHOD

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The WWR-K research reactor is multi-purpose and has a large number of vertical and horizontal irradiation channels with different geometric dimensions and neutron intensities. The presence of ten horizontal neutron beams in the WWR-K reactor and their incomplete loading makes the implementation of the boron neutron capture therapy (BNCT) method attractive. Boron neutron capture therapy (BNCT) is one of the most promising and effective cancer therapies in the world. However, it requires great efforts associated with the need to solve a number of complex problems. One of them is the creation of a neutron beam with specified characteristics suitable for therapeutic purposes. To use a neutron beam for therapeutic purposes, its quality must meet certain requirements in terms of neutron intensity, neutron energy distribution and neutron energy group ratio. For this purpose it is necessary to develop the design of the neutron beam forming facility. Modern software tools based on the Monte Carlo method make it possible to perform precision calculations and predict the expected experimental results. For the formation of a neutron beam with the properties required for BNCT, a special device is supposed to be installed in the experimental channel. This paper presents the results of numerical Monte Carlo simulations of various configurations of the beam-forming assembly of the WWR-K research reactor to determine the possibility of using BNCT. The influence of geometry and material composition of the beam-forming assembly on the spatial-energy distribution of neutrons and photons is shown. Technical solutions to optimise the radiation characteristics of the beam-forming assembly have been proposed. On the basis of the modelling, the optimal design of the WWR-K reactor beam-forming assembly has been selected.
The work was carried out with the financial support of the Ministry of Energy of the Republic of Kazakhstan under the scientific and technical programme № BR20081011. Keywords: BNCT, Monte Carlo method, BSA

Study of directional pulsed neutron flux generation for BNCT using a high intensity lithium beam

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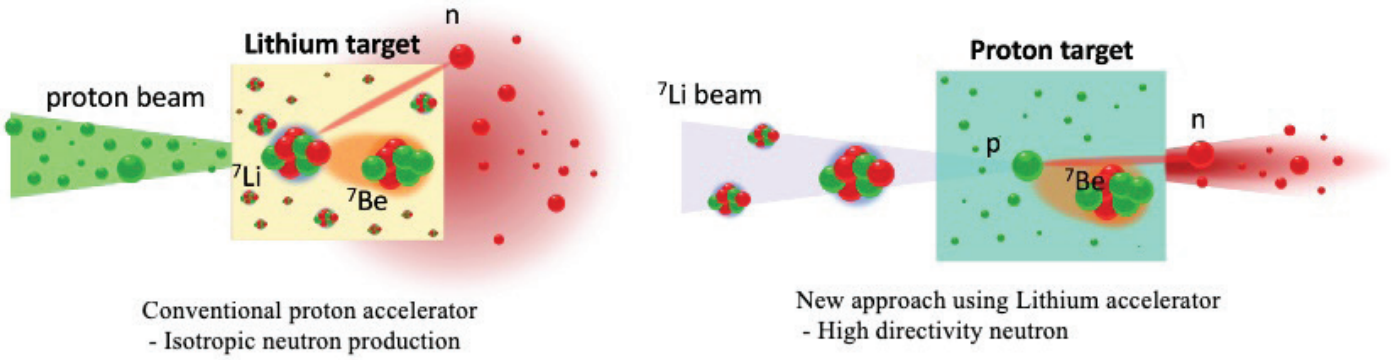

Figure 1. Isotropic and Inverse kinematic focusing

Basic BNCT research using reactors had been conducted at Brookhaven National Laboratory (BNL) previously. After the BNL BNCT research ended fifteen years ago, more effective drugs were developed, and the BNCT research is now concentrated in Europe and Asia. Clinical trials have already been initiated at several hospitals there but not in the U.S. We are proposing a system that uses a small accelerator to supply neutrons without generating unwanted radiation. In this system, fully stripped lithium ions are extracted from a high-density lithium plasma generated by laser ablation, accelerated by a small accelerator, and irradiating a hydrogen target to generate neutrons. All the accelerator-driven devices currently in operation or under consideration accelerate proton beams, and require massive shielding, because unwanted neutron radiation is emitted in all directions. However, if lithium is accelerated (instead of used as a target) and intersects with a hydrogen target (instead of used as a proton beam), the generated neutrons will be directed only in the forward direction due to momentum conservation, realizing a clean accelerator-driven neutron source [1]. In addtion, it may be possible to suppress unwanted radiation to patients further by separating the neutron-producing target and moderator. However, it has been difficult to supply high-intensity lithium ion beams, and their practical application of BNCT has been considered impossible.
Recently, we have conducted experiments on lithium beam generation using a method in which the plasma is injected directly into a linear accelerator. As a result, a peak beam current of 35 mA is obtained, which is much higher than that of conventional proton accelerator systems[2]. This demonstration verified the feasibility of a neutron generator for BNCT using an inverse kinematics scenario of neutron production. If we apply the reported neutron yield conversion [1] to our proposed neutron source, the average neutron flux can be scaled to about 7E9 n/s/sr with a 1 kHz repetition rate laser system, which is available in the market. In addition, it is possible to increase the yield of neutrons by further enhancing the laser.
At the congress, we will introduce our experimental results of lithium beam production and discuss possible configuration of neutron generator for BNCT.

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Keywords: CANS, RFQ, Laser, BNCT, Lithium

Acceleration of NCEP-MCX as a neutron dose calculation engine for NCT

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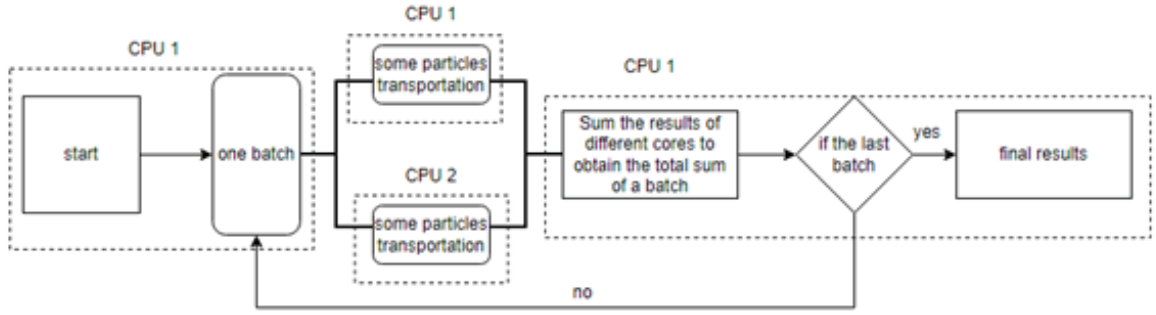

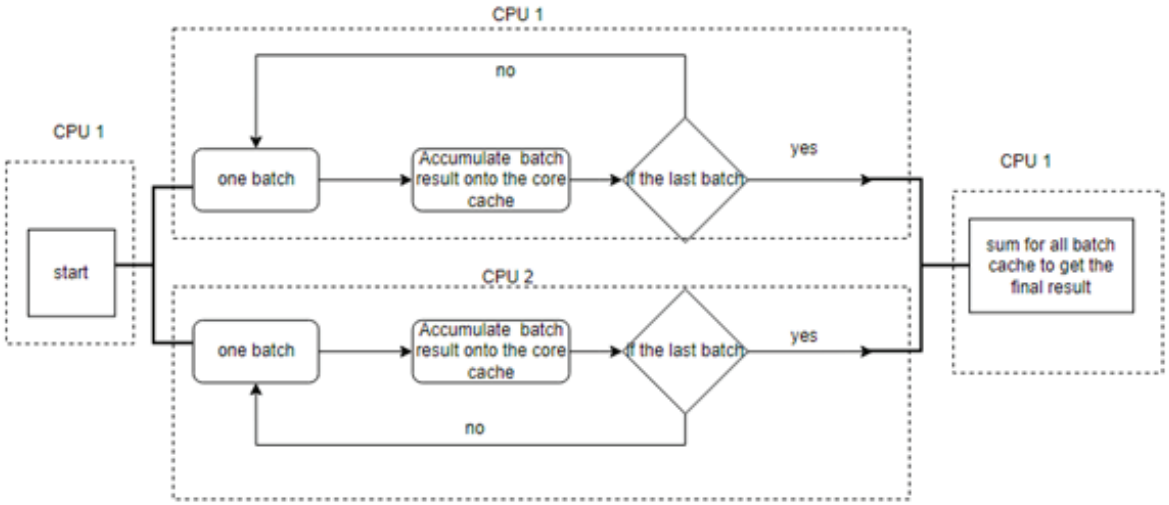

Acceleration methods	none	1	1, 2	1, 2, 3
Time of simulation/s	1307.377	625.684	317.324	242.784
Acceleration rate		2.089516433	4.12000668	5.38493888

1. Rapid tracking for rectangular voxel
2. Direct tally based on voxel mesh
3. Parallel method based on batch

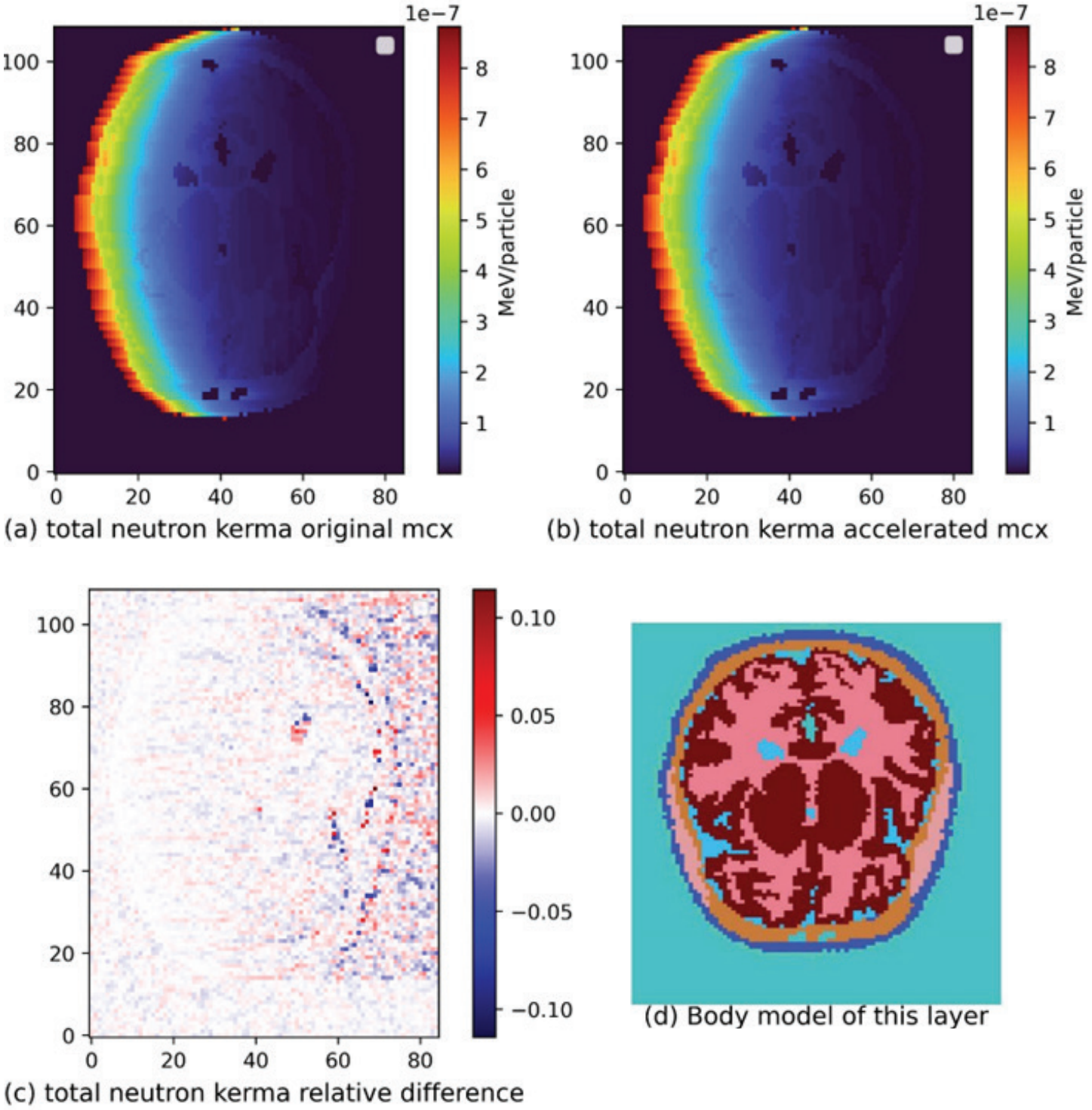

Figure captions:
Figure 1: The flowchart of different parallel methods
Figure 2: time comparison of different acceleration methods
Figure 3: comparison of the results between accelerated MCX and original MCX

During the process of Neutron Capture Therapy (NCT) for the treatment of cancer, it is essential to calculate the dose using a treatment plan system (TPS) prior to finalizing the treatment. The Monte Carlo simulation is commonly employed for dose estimation. However, the conventional Monte Carlo method may not meet the efficiency requirements for generating treatment plans. Thus, efforts have been made to accelerate the Monte Carlo method in three key aspects.
Firstly, in traditional Monte Carlo methods, a significant amount of time is consumed by surface crossing calculations, accounting for approximately 70% of the total transport time. The BNCT model, which consists of a structured voxel geometry with numerous voxel bins, necessitates a large number of surface crossing calculations based on the Constructive Solid Geometry (CSG) model. This leads to low computational efficiency. Hence, a new track tracing algorithm is proposed in this paper to enhance computational efficiency for dose estimation in treatment planning. Secondly, by performing surface crossing calculations, it is possible to obtain the track length within the corresponding voxel bins. As a result, we can directly tally the required quantities while evaluating surface crossings. This approach eliminates the need for tally mesh crossing calculations, thereby saving time during the tally process.

Thirdly, in the parallel calculation of the traditional Monte Carlo transport algorithm, statistical quantities need to be communicated and accumulated across the CPU cores for each calculation batch. This parallel strategy is depicted in Figure 1(a). However, for BNCT models with millions of voxel bins, the summation process can be time-consuming, while a sufficient number of batches is necessary to achieve accurate statistical deviations. To address this issue, this paper employs a batch-based MPI parallel strategy, as shown in Figure 1(b). Under this method, each core maintains a set of statistical quantities, allowing a batch computation to be performed within a single core without the need for a summation process. Once all batch computations are completed, inter-core communication is conducted to aggregate the statistical quantities across cores. This provides the total statistical quantities required for calculating the results and the corresponding statistical deviations.
The aforementioned acceleration methods have been implemented based on NECP-MCX[1]. To evaluate the effectiveness of these acceleration techniques, the total dose, N-dose, H-dose, and photon dose have been calculated for the Zubal head model[2]. Through the adoption of the three acceleration methods, the calculation speed has increased by 5.38 times. Figure 2 illustrates the comparison of calculation times and acceleration rates achieved with different acceleration methods. Furthermore, the dose estimations obtained from the original MCX and the accelerated MCX exhibit good agreement, as shown in Figure 3.

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Keywords: NECP-MCX, NCT, treatmentplanning, MonteCarlo

A GATE Monte Carlo study on ICRP110 phantoms for BNCT dosimetry evaluation

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Patient internal dosimetry is crucial for planning radiotherapeutic treatments. This involves estimating the absorbed doses not only to target lesions but also to surrounding healthy organs. Beyond treatment planning, internal dosimetry facilitates post-treatment analyses, enabling the deduction of dose-effect correlations on patient cohorts. In the context of Boron Neutron Capture Therapy (BNCT), patients are exposed to a complex radiation field. This field comprises neutrons from the beam, secondary charged particles (including ions) produced by neutron interactions within the patient's body, photons generated from these interactions, and residual photons originating from the accelerator and Beam Shaping Assembly (BSA). The unique composition of this mixed radiation field in BNCT presents a more intricate dosimetric challenge compared to conventional radiotherapies and radionuclide therapies. This complexity is further compounded by the varied radiobiological effectiveness of the particles involved. The use of Monte Carlo (MC) simulations is indispensable for BNCT dosimetry. These simulations allow for the estimation of different contributions to the absorbed dose. This data can then be used to compute the BNCT dose through the isoeffective dose formalism [1].
In this study, we used the GATE Monte Carlo toolkit, built upon the robust GEANT4 platform, to perform simulations replicating BNCT irradiation scenarios. The simulations were conducted on voxelized anthropomorphic phantoms, specifically employing the ICRP 110 Adult Reference Computational voxelized phantoms [2]. The primary objective was to investigate, using these standardized phantoms and initially focusing on simplified neutron beam settings, the dose contributions to organs of interest under various parameters. These parameters included neutron energy, beam direction, distance from the volumes to be irradiated, and the concentration of ^{10}B in the organs of interest.
Considering the ongoing construction of a BNCT facility at the University of Campania "Luigi Vanvitelli" in Caserta, Italy, funded within the framework of the PNRR-PNC ANTHEM project, with an initial focus on treating brain and head/neck malignancies, our research specifically targeted the simulation of head irradiation. To achieve this, we concentrated our efforts on simulating the irradiation of the head, specifically focusing on the brain organ of the ICRP110 phantoms. In preparation for these simulations, we developed ICRP110 phantom files compatible with the GATE Monte Carlo toolkit. This involved configuring the appropriate material compositions and densities for each organ, aligning with the specifications outlined in [2]. Additionally, to further refine our analysis, we introduced ^{10}B fractions to the standard brain composition.
The preliminary results presented involve a comparison between Gate v9.1 and MCNP v6.3 simulations, evaluating GATE's performance. This assessment was conducted using both monoenergetic and realistic neutron beams. Throughout these simulations, a comprehensive analysis was undertaken by scoring various quantities to compute the total absorbed doses per source particle. This involved the breakdown of the separate dose components crucial in the context of BNCT treatments. These components are alpha particles and ^{7}Li generated through neutron capture on ^{10}B (boron component), protons emerging from neutron interactions with nitrogen and hydrogen (neutron component), and photons produced in the neutron beam and by neutrons interacting with the patient's body (photon component). This comparative study aims to provide insights into the effectiveness and reliability of Gate v9.1 in replicating BNCT scenarios when compared to MCNP v6.3 simulations.

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Keywords: BNCT; internal dosimetry; Monte Carlo;antropomorphic_voxelized_phantoms

Machine learning based image classification and segmentation in neutron autoradiography

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In recent years, machine learning methods have gained popularity in the fields of life and medical sciences. At research level, both in-vivo and ex-vivo techniques apply these algorithms not only for classification but also for segmentation and tracking objects. In the context of BNCT, information derived from boron imaging techniques holds significance in various areas, from assessing new boron compounds to predicting patient outcomes. In our laboratory, we have developed several approaches of neutron autoradiography to asses boron localization at tissular and cellular level. The current procedure employed in the laboratory for the generation of autoradiographic images consists on the irradiation of the nuclear track detector (NTD) in contact with a biological sample previously infused with a boron compound, with thermal neutrons. Subsequently, a histological observation is carried out, delineating areas of interest. Then, a chemical attack is performed to amplify the tracks and allow their observation through optical microscopy to perform a quantification in the pre-selected areas [1].
In the first place, we developed a supervised learning algorithm for the classification of adequate and inadequate images acquired on the NTD. The goal was to identify images obtained under inadequate conditions and optimize the quantitative autoradiographic analysis. This process involved creating a dataset of distributions of representative morphological and greyscale uniformity parameters of individual tracks extracted from bright field optical microscopy images. These parameters included area, diameter, aspect ratio, roundness, heterogeneity, and clumpiness. Statistical parameters were calculated for each of the six characteristics, resulting in a total of 36 features. Each image was assigned a classification label, either “Accepted” or “Rejected,” based on the classification criteria of an autoradiographic images expert. Various machine learning models were evaluated and the two which exhibited the highest performance were a Support Vector Machine and an fully-dense Artificial Neural Network (NN), demonstrating an overall performance comparable to that of a trained expert in classification (around 93%). Considering the distribution of predicted class probabilities, which roughly indicates the confidence of the algorithm in its classifications, the NN demonstrated a superior ability to identify and discard inadequate images. Consequently, the NN was selected to carry out the image verification step before quantification. The trained NN exhibited accurate classification of images, regardless of their track density [2].
In order to increase the spatial resolution, another approach involves the sensitization of polycarbonate detectors with UV-C radiation in order to generate biological imprints of cell cultures [3]. Since this irradiation modifies the chemical attack kynetics, the shielding produced by the sample allows the simultaneous observation of the biological structure and the nuclear tracks.
The generated imprint complicates the autoradiographic image, introducing a background that hinders track quantification. For this reason, this work proposes the use of a convolutional neural network for track segmentation, creating masks that can later be used for microdistribution analysis by delimiting cells through the imprints. Based on a literature search, a U-NET was decided to be implemented. This architecture is commonly used in medical image segmentation and optimized for achieving more precise results with fewer images, employing a architecture of contraction and expansion layers. The selected metrics to evaluate the segmentation performance were mean intersection over union and mean dice. Both metrics take into consideration the unbalance of pixels belonging to each class (background or track, with the possibility of adding more classes if decided to incorporate the segmentation of cells).
The implementation proved promising and is currently being compared with results obtained using commercial software. In this work, we will present the different implementations of machine learning for both classification and segmentation purposes carried out at our laboratory.

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Keywords: machine learning, classification, segmentation, neutron-autoradiography,boron-imaging

Re-evaluation of Neutron Spectrum in Heavy Water Neutron Irradiation Facility of Kyoto University Research Reactor using Simple Multilayer Spectrometer

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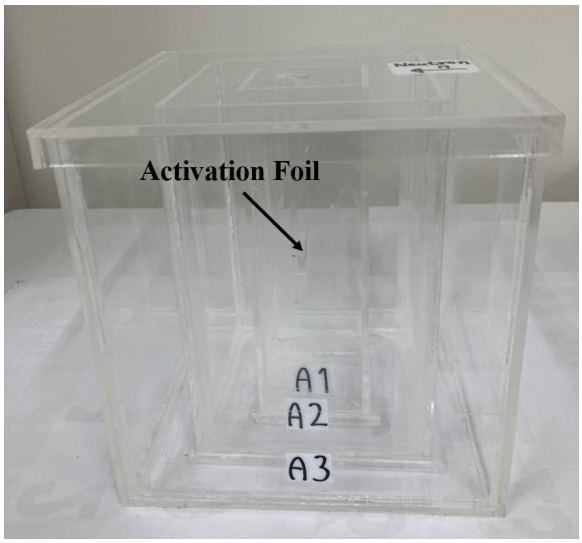

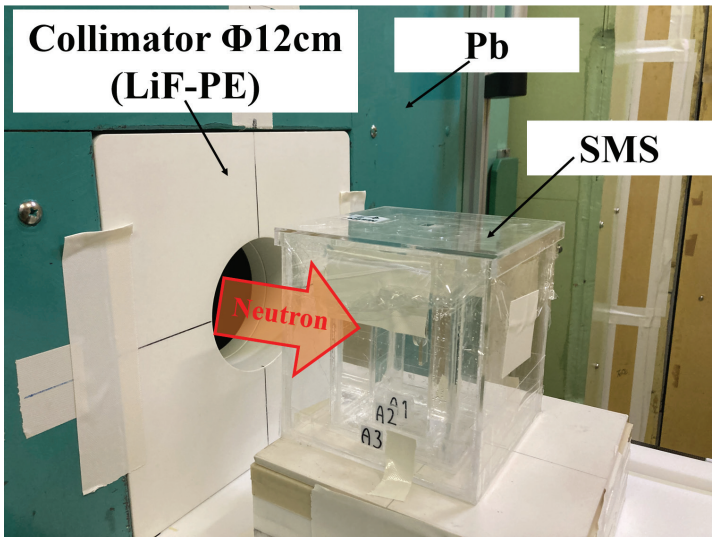

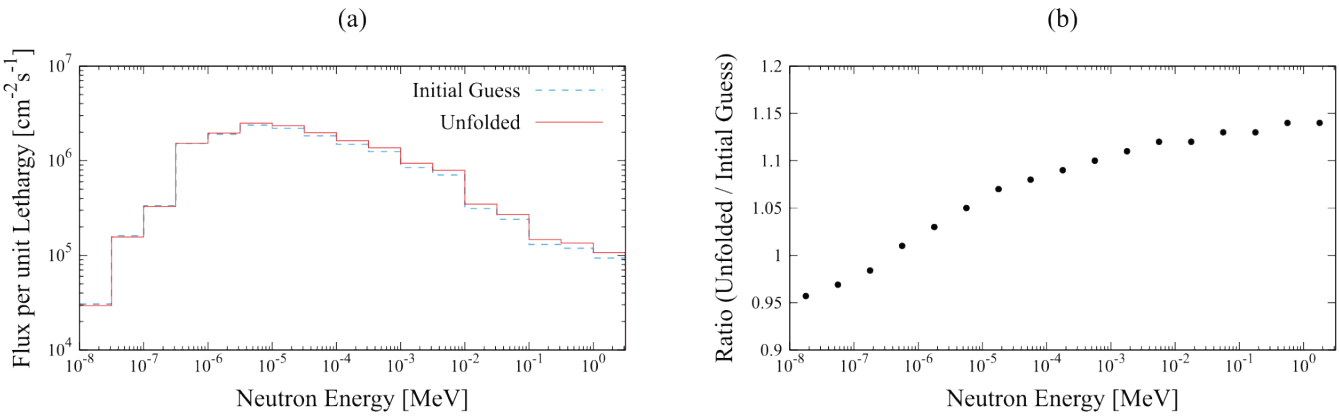

Figure captions:
Figure 1: Structure of SMS
Figure 2: SMS irradiation experiment setup
Figure 3: Evaluated neutron spectrum (a) initial guess and unfolded result (b) ratio between unfolded result and initial guess

Information on the neutron spectrum of the BNCT irradiation field is required for the calculation of equivalent doses in treatment planning. Moreover, the verification of the beam-shaping system can be confirmed based on the evaluated neutron spectrum result. We recognize that the evaluation of the neutron spectrum in the BNCT neutron irradiation field needs to be accurately conducted.
The Heavy Water Thermal Neutron Facility (HWTNF) of Kyoto University Research Reactor (KUR) had been operational in the irradiation field for BNCT since 1974. Following a facility construction update in 1996, the facility name was changed to Heavy Water Neutron Irradiation Facility (HWNIF) and the neutron spectrum was evaluated using the multi-foil activation method (Sakurai and Kobayashi, 2004). In 2010, KUR transitioned its operation from high-enrichment fuel (HEU) to low-enrichment fuel (LEU). However, the neutron spectrum in KUR-HWNIF has not been re-evaluated since then.
We have investigated the Simple Multilayer Spectrometer (SMS) for measuring the neutron spectrum in the BNCT irradiation field. Recently, many neutron spectrometers were developed with the concept of changing liquid moderator injection patterns to differ the response function. We incorporated this idea into our developed SMS spectrometer. Activation foils placed at the center of the SMS were utilized as neutron detectors. In this study, we aimed to performed neutron spectrum re-evaluation in the epithermal neutron irradiation mode at KUR-HWNIF by using SMS.
Figure 1 shows the SMS, including different-sized liquid moderator containers and activation foil which placed at the center. Containers have dimensions of 5cm×5cm×15cm (A1), 10 cm×10cm×15cm (A2), and 15cm×15cm×15cm (A3), respectively.

Three spaces between each container are utilized to inject liquid moderator. In the SMS, pure water and boric acid water were used as liquid moderators. Additionally, an empty space was also included. With the structure of SMS, we can receive maximum of 27 injection patterns. However, conducting all injection patterns in measurements is time-consuming and inefficient. Based on our previous optimization which promised to give high accuracy neutron spectrum evaluation result (Prateepkaew et al., 2024), only 6 injection patterns with high energy resolution response function were selected.
Figure 2 shows the experimental setup for SMS measurements in the KUR-HWNIF. After irradiation of SMS, the specific saturated activity of the irradiated activation foils in 6 injection patterns were measured. From the measurement results, we can estimate the neutron spectrum of measured neutron irradiation field by using the unfolding method. In this research, GRAVEL code was used to perform spectrum unfolding (Reginatto, 2004). For the GRAVEL code, user need to provide the initial guess of the solution. In this case, we use the previously-evaluated spectrum for the epithermal irradiation mode of KUR-HWNIF after passing through the collimator as the initial guess.
Figure 3(a) shows the initial guess and unfolded neutron spectrum result at 15.5-cm distance from collimator surface position. To analyze the difference between initial guess and unfolded neutron spectrum result, ratio between unfolded neutron spectrum result and initial guess was calculated which shown in Figure 3(b). According to Figure 3(b), the range of the ratio was 0.96-1.14, and the ratio increased with higher neutron energy. This re-evaluated spectrum information holds significance for the BNCT research at KUR-HWNIF.

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Keywords: Neutron Spectrum, Neutron Spectrometer, Unfolding

Fluorescent Nuclear Track Detectors (FNTD) application for Boron microdistribution reconstruction in biological samples

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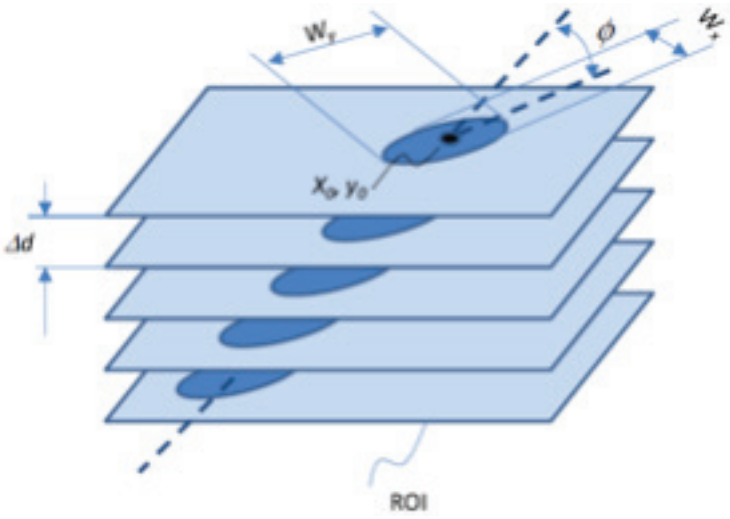

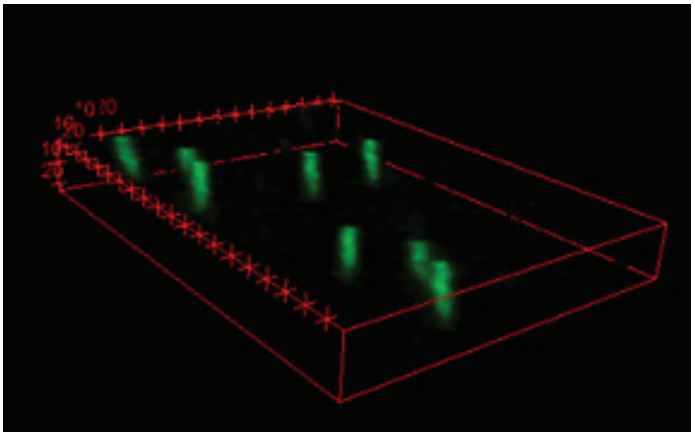

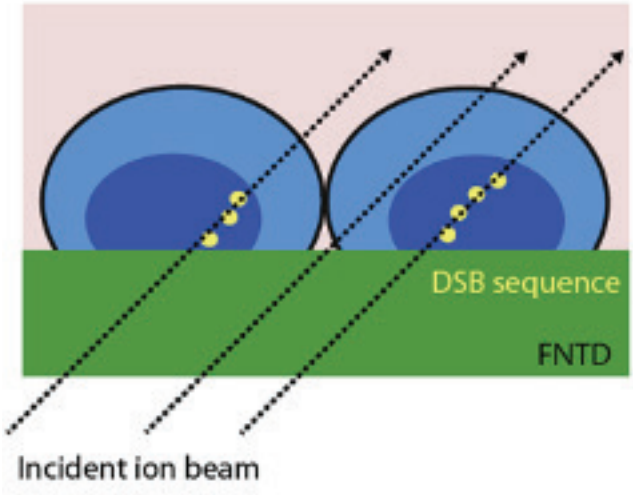

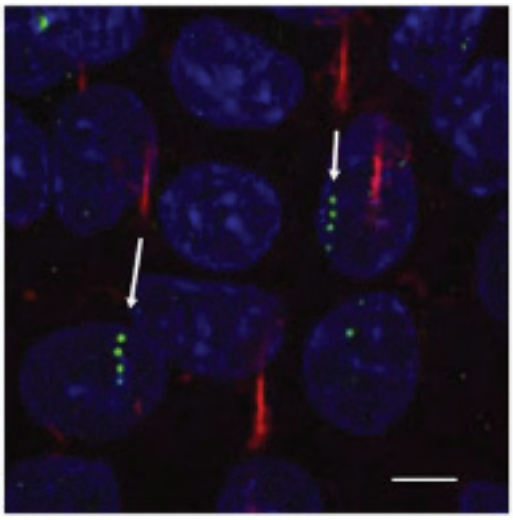

Figure captions:
Fig.1: Processe of image stacking [2].
Fig.2: (L) depiction of the acquired stack close to the detector surface; (R) superposition of cellular response [3].
Fig.3: 3D reconstruction of Am241 α-tracks.

Fluorescent Nuclear Track Detectors (FNTDs) have been analyzed as possible detectors in order to study the ^{10}B spatial distribution at subcellular level, a crucial information to evaluate the BNCT effectiveness. FNTD technology is based on a single crystal of aluminum oxide doped with carbon and magnesium impurities (Al_2O_3:C,Mg). The afore mentioned impurities generate special fluorescent structures known as F_2^{2+}- centers, which have an absorption band at 435 nm that give the detector its yellow color. These centers easily absorb the free electrons produced during an irradiation. Consequently, they undergo photochromic and radiochromic transformations into a three-electron state, forming the F$_2^+$- centers. The reading of the detector in the Confocal Laser Scanning Microscopy (CLSM) technique exploits the excitation (~620 nm) and emission (~750 nm) bands of these centres [1]. This technique provides a high spatial resolution and enables the discrimination between the fluorescence induced by a tight focal laser spot within the track volume, and the background fluorescence caused by the laser beam in the surrounding crystal volume. The FNTD's read-out is non-destructive, with no charge recombination, allowing multiple detector readings. Additionally, to reduce the background luminescence, detectors experience thermal annealing with a specific heating profile and optical bleaching. The latter procedures can be replicated to erase fluorescent tracks, permitting the FNTDs' reuse. With CLSM technique a series of images of the same detector area at different depths are acquired. A software analyzes this sequence within a chosen region

of interest (ROI), which contains traces resulting from particles transit. Each bright element of a stack slice is fitted to a 2D Gaussian, generating the following output parameters: the fluorescence intensity amplitude (A), the background fluorescence (B), the centroid coordinates (x_0,y_0), the track amplitudes (Wx,Wy) and the incident angle (ϕ) (Fig.1) [2]. Another important feature of these detectors is their biocompatibility; this makes it possible to deposit and grow a cell layer on them and subsequently study the effects produced by irradiation with ionising radiation (Fig.2) [3]. A further enhancement of this hybrid detector is the Cell-Fit-HD4D structure that monitors the cell layer over time after the irradiation. It observes whether DNA damage produced at a single-cell level, leads to the cell death or to cell proliferation [4]. The aim of our work was to apply, for the first time, these detectors to study the 10B spatial distribution at subcellular level. The work has been conducted in collaboration and with the support of the Medical Physics in Radiotherapy Department of German Cancer Research Centre of Heidelberg. Using the SRIM code [5], we simulated the formation of the tracks produced in the detector by the alpha particles and Li nuclei emitted in the ^{10}B(n,alpha)^{7}Li capture reaction; we then experimentally characterised the detector's response to these particles. The alphas emitted by the ^{241}Am were used as an initial step. Fig. 3 shows the three-dimensional reconstruction of some of these traces. Subsequently, to study the detector's response to alpha particles with an energy closer to those emitted in BNCT, a 23 µm mylar foil was interposed between the source and detector. As a final step, a ^{10}B standard was used, placed in contact with the detector and irradiated with neutrons in the thermal column of the Triga Mark II reactor of LENA at the University of Pavia. The trajectories of alpha particles produced in the capture reaction have been successfully visualized. Preliminary results of this work will be presented in the talk.

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Keywords: FNTD, boron, imaging, concentration, microdistribution

Radiation protection calculations in the design of an AB-BNCT facility: neutron activation and dose-rate after the accelerator shutdown.

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In the framework of the PNC-PNRR ANTHEM project, a new Accelerator-Based Boron Neutron Capture Therapy (AB-BNCT) research and clinical facility will be built in Caserta, Italy. This facility will be based on a Radio Frequency Quadrupole proton accelerator, designed and manufactured by the Italian National Institute of Nuclear Physics (INFN), coupled to a beryllium target. This machine delivers 5 MeV protons with a 30 mA current in continuous wave, producing at the target a neutron flux of the order of 1014 neutrons per second. Radiation protection calculations play a critical role during the design of an AB-BNCT facility. In this context, in our group, simulations of the clinical irradiation in the ANTHEM facility have been performed to evaluate the quantities of interest concerning dosimetry and neutron activations. To do that, the geometry of the facility has been reproduced using different Monte Carlo transport codes. In particular, using the codes PHITS and DCHAIN, we have calculated the dose-rate at different times after the accelerator shutdown. We have considered the neutron activation of the Beam Shaping Assembly (BSA) and the neutron activation of the walls in the treatment room. The obtained results allowed us to know the principal radioactive isotopes in the BSA and in the walls as a function of time. For each time, we have also calculated the ambient equivalent dose rate. Additionally, we have investigated the residual specific activity of air within the irradiation room, giving special attention to the neutron activation of Ar-40, that produces the beta-emitter Ar-41 with a half-life of approximately 109 minutes. In this case the specific concentration of the Ar-41 as a function of time was calculated considering also the recirculation of air. The studies performed in this work, together with additional radiation protection studies carried out by our research group were pivotal in defining the design of the ANTHEM facility and will be fundamental for the management of the future patients after the BNCT treatment.

Keywords: Radioprotection, Neutron, activation, BSA, walls

Preliminary Exploration of 2D Reaction Rate Measurement Method based on Indirect Neutron Radiography in BNCT

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Comprehensive characterization and validation of the neutron beam is paramount for the success of Boron Neutron Capture Therapy (BNCT). Instrumental Neutron Activation Analysis (INAA) is the most commonly used method for neutron beam characterization. It characterizes neutron flux, energy spectrum, and spatial distribution by measuring the reaction rates of activation detectors. However, INAA primarily offers point measurements, and consequently, a series of measurements at different points is required to fully characterize the neutron beam parameters, making the process time-consuming and labor-intensive. This study aims to develop a two-dimensional (2D) reaction rate measurement method based on indirect neutron radiography (INR) and to conduct preliminary verification of its accuracy. A specialized INR method platform was developed at the Xiamen Humanity Hospital-Neuboron BNCT Center. It mainly comprises an Imaging Plate (IP), a readout device, activation detectors (copper foils), and a real-time temperature monitor. To ensure the accuracy of the INR method, the impacts of ambient temperature and fading time on the IP signal were investigated using the platform. By using the activation foils, the study established a correlation between the IP signal and dose deposition. This procedure determines the reaction rates by correlating the IP signal to dose deposition and then relating it to the induced activity. The accuracy of the INR method was confirmed by measuring the reaction rates of copper strips and plates placed inside a PMMA phantom and exposed to the epithermal neutron beam of the NeuPex system. These results were critically compared with results obtained from the conventional INAA method. The study revealed that the IP signal is minimally affected by ambient temperature, with a 1-degree change resulting in less than 0.1% variation. However, the IP signal linearly decreases over time due to fading. Consequently, it is crucial to control temperature and to correct for signal decay when applying the INR method. Additionally, the relationship between the IP signal and dose deposition can be mathematically expressed as y = (20500×x^0.01803)-21103. In applying the INR method to measure the reaction rate of copper strip, the depth distribution trend is consistent with the results obtained through the NAA method to within 5% relative deviation for a 4 cm depth range of the copper strip. The initial results indicate significant potential for the INR method in 2D reaction rate measurement for BNCT. Future research will focus on reducing measurement errors from various factors, ultimately aiding in the rapid characterization of the BNCT neutron beam.

Keywords: BNCT, INR Method, Reaction Rate

Progress in the development of dosimetry tools for boron neutron capture therapy

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An accelerator-based neutron source VITA has been proposed and created at the Budker Institute of Nuclear Physics in Novosibirsk, Russia [1]. Neutrons are generated in the $^{7}Li(p,n)^{7}Be$ reaction at a proton energy of 2.3 MeV. A beam shaping assembly with MgF_2 moderated is used to produce a therapeutic neutron beam. The first VITA facility is used in Novosibirsk for the development of BNCT, the second facility is used in the Xiamen Humanity Hospital BNCT Center (China) for clinical trials, the next two facilities are manufactured for the National Center for Oncological Hadrontherapy in Pavia (Italy) and the National Medical Research Center of Oncology in Moscow (Russia). Since many new BNCT centers are expected to appear soon, the development of dosimetry tools for characterization of therapeutic mixed neutron-photon beam and assessing the patient's response to treatment is becoming relevant. In this work, a number of dosimetric techniques have been developed: a compact neutron detector with a pair of cast scintillators, one of which is enriched with boron, to measure the boron dose and the gamma-ray dose; cell dosimeter for measuring the sum of the equivalent dose of fast neutrons and the equivalent nitrogen dose; epithermal neutron flux monitor for measuring the epithermal neutron flux; prompt gamma-ray spectroscopy for in situ measurement of boron dose in real time. Their verification carried out on the accelerator based neutron source VITA showed the following. The compact neutron detector has proven to be a simple, reliable tool for measuring boron dose and gamma-ray dose in air or in a water phantom and should be equipped with facility to confirm the quality of the therapeutic beam. The cell dosimeter, although labor-intensive to implement, provides reliable information on the contribution of the other two remaining doses - the fast neutron dose and the nitrogen dose. Numerical neutron transport simulation shows that the epithermal neutron flux monitor is sensitive to epithermal neutrons and it has a flat sensitivity curve in epithermal neutron range, while its sensitivities to thermal and fast neutrons are low. The method of prompt gamma-ray spectroscopy, proposed 40 years ago [2], was successfully implemented at the facility when treating domestic animals with spontaneous tumors. It provided new information on the dynamics of boron accumulation different from the prevailing ideas. The results obtained made it possible to determine the absolute value of the absorbed dose, which is very important for assessing the result of therapy. The report will also briefly provide information on the results of measuring the cross section of nuclear reactions, testing new boron delivery drugs and on research on the implementation of lithium neutron capture therapy, which brings a new quality – 100% release of nuclear reaction energy in tumor cells. This research was supported by Russian Science Foundation, grant No. 19-72-30005.

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Keywords: neutron capture therapy, neutron source

Feasibility study of extremely small BNCT system: Storage ring based compact BNCT System using the $^{3}H(d, n)^{4}He$ reaction

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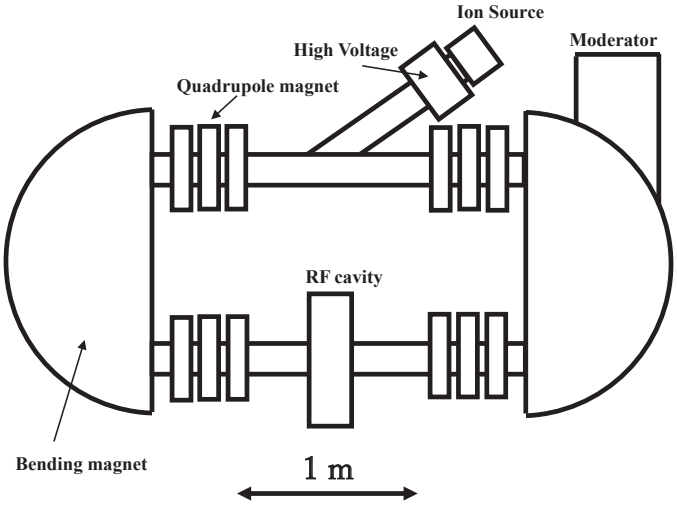

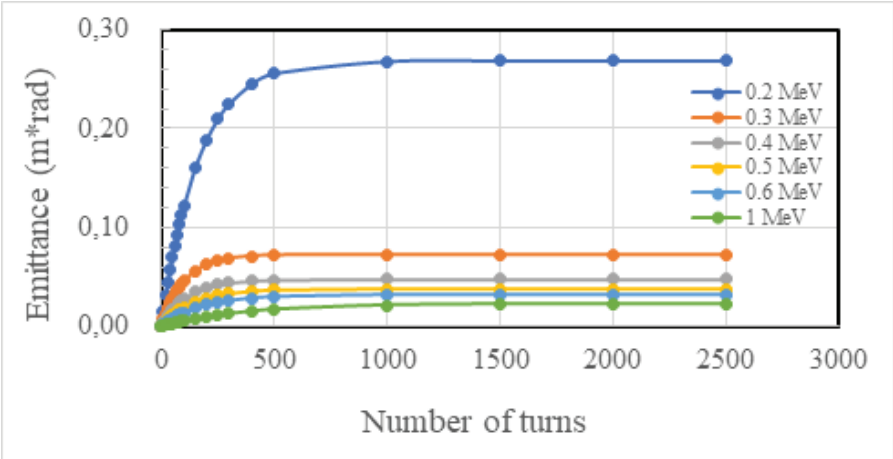

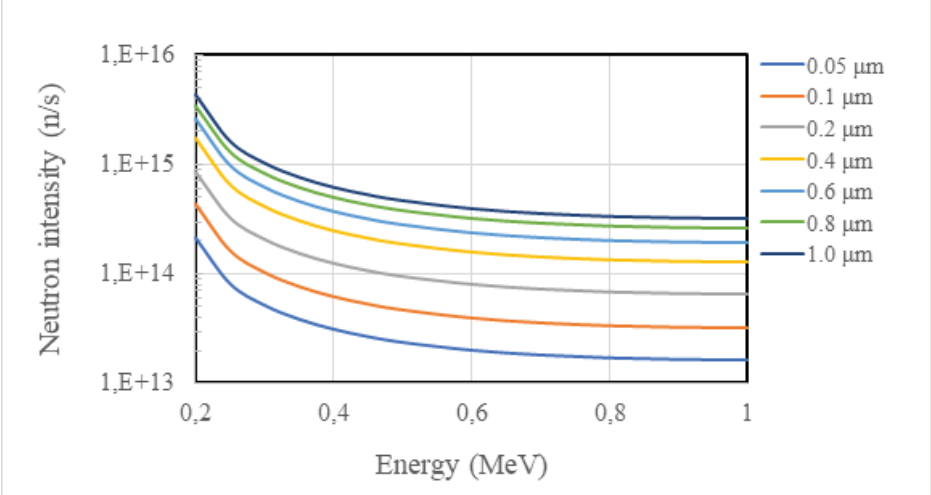

Figure captions:
Fig. 1 Concept of the compact storage ring based BNCT system.
Fig. 2 Emittance growth of the deuteron beam in the compact storage ring.
Fig. 3 Neutron intensity produced by the 3H(d, n)4He reaction.

Cyclotrons are used in accelerator-based BNCT systems because their neutron yield increases with incident proton energy [1]. Although linear and static accelerator-based BNCT systems are being developed for smaller systems, these accelerators are still large compared to conventional medical devices. If the lower energy particles can generate enough neutrons, the accelerator will become smaller, resulting in a compact BNCT system. Such systems require beam currents on the order of amperes to generate enough neutrons to treat a patient, which is very difficult to achieve. However, if the particles are stored in the storage ring and repeatedly collide with the internal target, sufficient neutron yield can be achieved even with the low neutron intensity produced by a single-pass beam. Figure 1 shows the concept of the compact storage ring based BNCT system. The deuteron beam is stored in a storage ring, passes through the target, and produces neutrons by the $^{3}H(d, n)^{4}He$ reaction. This reaction only requires accelerating the deuterons to a few hundred keV, making it possible to reduce the size of the storage ring. To confirm whether this idea is actually possible, we calculated the number of deuterons stored in the storage ring and the intensity of the generated neutrons.

In the storage ring, the deuteron beam is focused by a quadrupole magnet, but as the beam current increases, the divergence force increases due to space charge forces. Assuming that the deuteron beam can be stored until the space charge force becomes greater than the focusing force, we derive an expression for the maximum number of deuterons that can be stored. Since the maximum number of deuterons is proportional to the deuteron emittance determined by heating and energy loss due to multiple scattering by the target and cooling due to RF acceleration, we calculated the increase in the emittance of the deuteron beam. The result is shown in Fig. 2. The calculations assumed a thin-film titanium target with a thickness of 0.05 μm that accumulates twice as many tritium atoms as titanium atoms. The figure shows that the energy of the deuteron beam must be greater than 0.3 MeV because the emittance of the 0.2 MeV deuteron beam is too large to accumulate in the ring. The deuteron beam is heated and cooled also in the longitudinal direction, and its energy spreads with each revolution. We calculated this energy spread. The results showed that the relative energy spread increases with the deuteron energy and exceeds 10% at 0.45 MeV. These results indicate that the deuteron energy must be greater than 0.3 MeV and less than 0.45 MeV. The neutron intensity is proportional to the cross section of the $^{3}H(d, n)^{4}He$ reaction, the number of target atoms, the film thickness, the revolution frequency, and the number of accumulated deuterons. The neutron intensity was calculated using the maximum number of deuterons derived. Figure 3 shows the results for thin film targets with thicknesses between 0.05 μm and 1.0 μm. For treatment, the neutron intensity must be greater than 5×10^{13} n/s. It can be seen that the neutron intensity satisfies the conditions for treatment in the energy range of 0.3 MeV to 0.45 MeV, where the emittance and energy spread are acceptable.

In conclusion, it is possible to obtain neutron yields exceeding 5×10^{13} n/s in a compact storage ring, and the realization of compact storage ring based BNCT is expected. We would like to add that rings half the size may be possible by further study.

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Keywords: Storage ring, Cooling, Internal target

Development of the BNCT treatment planning functions based on NECP-MCX

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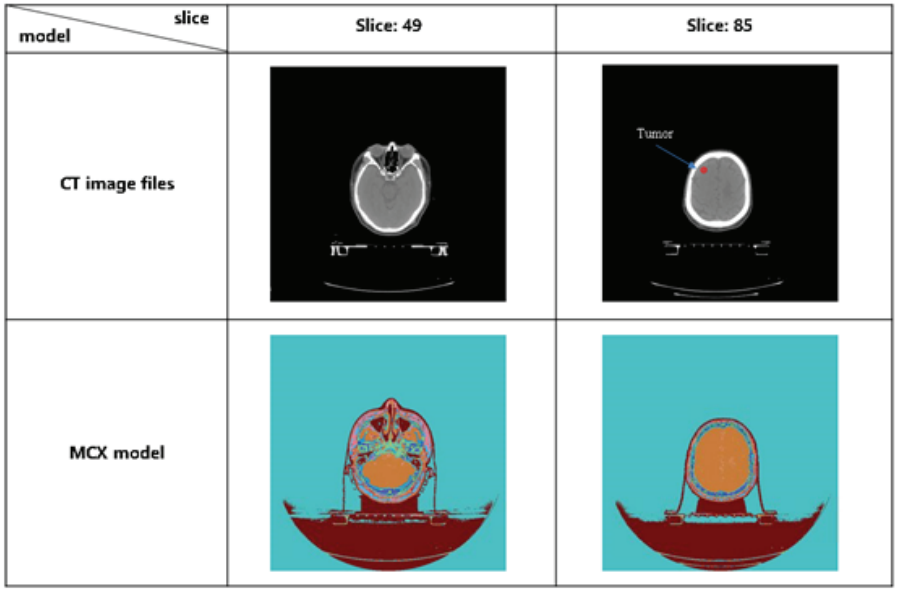

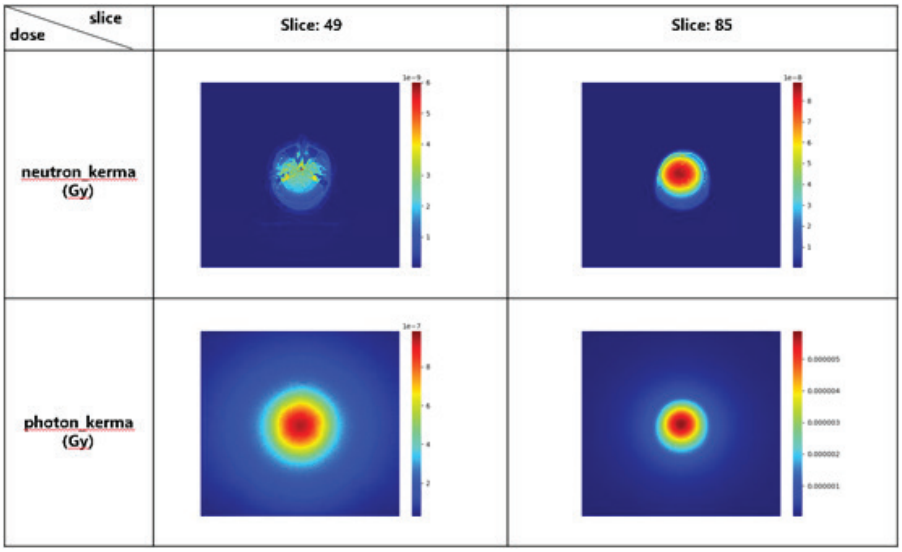

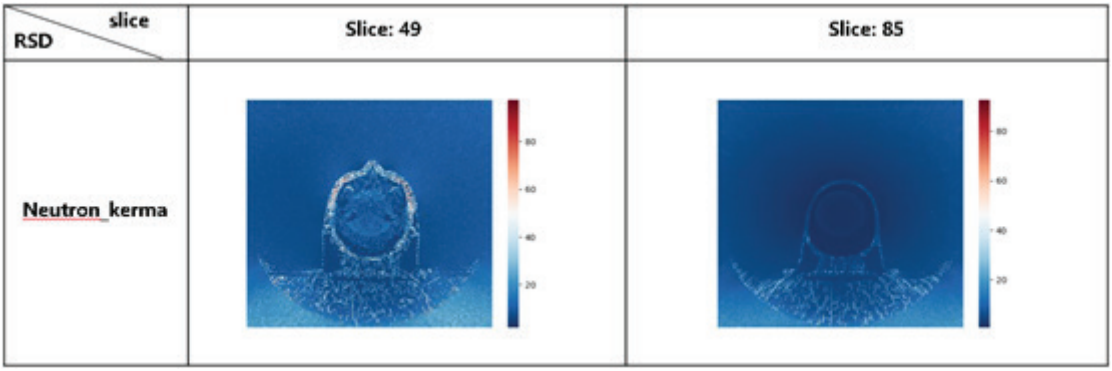

Figure captions:
Figure 1. Slices of CT images and MCX model
Figure 2. Distribution of neutron dose and photon dose in slices
Figure 3. Relative standard deviation of neutron dose in slices

In the Boron Neutron Capture Therapy process, a suitable treatment planning system is crucial for dose calculation and plan

specification. Based on the in-house Monte Carlo neutron-photon transport software NECP-MCX[1], this research has developed the special functions for treatment planning. The software includes native support for the DICOM protocol through the introduction of DCMTK, automatic 3D voxelization modeling of phantom files[2, 3, 4], and automatic data post-processing and evaluation, such as dose volume histogram (DVH) generation. NECP-MCX can now complete the formulation and verification of the BNCT treatment plans in a standardized manner.

A numerical experiment was developed for a specific patient case in this research. A three-dimensional voxelization model of the head was build based on the Hounsfield Unit (HU) values extracted from the patient's CT image. The number of voxel grids reaches to 28835840. As shown in the Figure 1, slices of the CT images and the cross-sections of the calculation model at two typical locations are selected and displayed. Slice 49 can show a complex human structure, and slice 85 is the largest cross-section of the patient's tumor. The source beam of the therapy case has a single direction from top to bottom, with 5cm diameter. The energy spectrum consists of three components: 10% thermal neutrons, 89% epithermal neutrons and 1% fast neutrons, with each component following a typical 1/E spectrum. The case is running under 2048 batches on a 64-core computer, each batch has 1×10^5 particles, with a total of 200 million particles.

The calculation completed with only 24 minutes with the tally results of the three-dimensional dose distribution of the entire model. The neutron dose, photon dose and their relative standard deviation(RSD) are given accordingly in Figure 2. Figure 3 shows the RSD of neutron dose at different slices. For slice85, RSD of the calculated results is no more than 10% in 87% of the voxel grids and no more than 20% in 98% of the voxel grids. For slice49, RSD of its calculated results was no more than 10% in 63% of the voxel grids and no more than 20% in 89% of the grids. Further, for entire 3D voxel model, RSD of the calculated results is no more than 10% in 52% of the voxel grids and no more than 20% in 83% of the voxel grids. It shows that the reliability of NECP-MCX is enough, and the performance of complex human body structures in deep depth is also excellent. The above results demonstrate that NECP-MCX can perform BNCT dose calculation accurately and efficiently, confirming its feasibility in solving radiotherapy dose-related challenges. Further verification will be conducted with additional numerical examples as part of ongoing development and functionality improvements.

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Keywords: BNCT, NECP-MCX, dose calculation, DICOM

Design and Performance Analysis of Electron Accelerator based Full-Spectrum Neutron Source

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Electron accelerator-driven white neutron sources have the advantages of low cost, compact structure, moderate flux, and high time-of-flight measurement accuracy, making them highly promising in various application fields and irreplaceable by other neutron sources. The modification of an electron accelerator into a white neutron source involves multiple steps, including adjusting the accelerator energy, changing beam intensity, selecting appropriate target materials and optimizing the neutron source. In this study, the full beam transport process from the electron gun to the neutron target in an electron linear accelerator was simulated using the Geant4 tool. The neutron production from different target materials under the impact of electron beams was investigated. The accelerator used in this study is a traveling wave electron linear accelerator capable of providing three different electron beam energies: 6 MeV, 8 MeV, and 10 MeV, with an average beam power of 5 kW and corresponding beam intensity of 0.5 mA. The geometry of the target consists of a combination of cylinders and cones, and materials such as tungsten, heavy water, lithium, beryllium, and their compounds were chosen for the neutron source. Through simulation, we obtained data on neutron yield, neutron energy spectra, spatial distribution, and temporal characteristics when different energy electron beams directly bombard different target materials. This data provides support for the modification of electron accelerators into white neutron sources. We also demonstrated that adding a specific-shaped graphite reflector can increase the forward emission of neutrons. By comparing the angular distribution of neutron flux in the forward direction before and after the addition of the reflector, the optimization effect of the reflector on the neutron source is clearly observed. In conclusion, this research provides a foundation for the modification of electron accelerators into white neutron sources through simulation and data support. It also demonstrates the effective optimization of neutron sources by adding specific-shaped graphite reflectors. This has significant implications for the application and technological development of white neutron sources.

Keywords: Electron accelerator,full-spectrum neutron source,geant4

Calculation of Accelerator Based Neutron Sources and Beam Shaping Assembly with Genetic Algorithm

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The beam shaping assembly is a core component in processing neutrons for Boron Neutron Capture Therapy (BNCT), capable of moderating fast neutrons to thermal and epithermal neutron energy regions (0.5 eV < En < 10 keV), and filtering out harmful components in the beam. This paper utilizes the Monte Carlo program GEANT4 to calculate the neutrons produced by bombarding tungsten targets with electron beams of 6MeV, 8MeV, and 10MeV. The primary goal is to find an optimal geometric configuration in the tungsten target position design that maximizes neutron production efficiency and yield. Since different neutron energy spectra are produced by bombarding tungsten targets with electrons of various energies, different BSA designs are required, and there are differences in treatment effects and penetration depths. Therefore, this paper uses the high-dimensional multi-objective optimization performance of the Nondominated Sorting Genetic Algorithm III (NSGA-III) in combination with GEANT4, targeting neutron beam parameter values recommended by the International Atomic Energy Agency (IAEA) for BSA optimization. The optimized designs enable the epithermal neutron beam parameters to meet IAEA recommendations, characterized by high epithermal neutron flux and low contamination. At the same time, the designs offer compact volume and optimal moderation performance. The Snyder head model is employed to evaluate the clinical dosimetric parameters of each design, analyzing the treatment effects. Based on the optimal treatment effects and depths, the study attempts to summarize the best BSA for neutron energies in different intervals, establishing reference formulas for neutron therapy effectiveness across different energy ranges. This provides a reference for scientific research and clinical treatment. The computational results not only meet treatment requirements with a compact overall BSA device volume and low shielding costs but also provide BSA structures suitable for different energy neutrons produced by bombarding tungsten targets with electron beams in the 6-10MeV energy range. This establishes reference formulas for treatment effects, offering a strong reference for developing clinical treatment plans. It also shortens computation time and improves computational efficiency.

Keywords: BNCT, BSA, Geant-4, NSGA-III

POSTER PRESENTATIONS

Session 1

S1P1

The level of circulating myeloid-derived suppressor cells as an index to predict the therapeutic effect of BNCT in glioblastoma (GBM) patients

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Glioblastoma multiforme (GBM) is one of the most common malignant brain tumors. It has a poor prognosis causing the extremely resistant to current therapy including surgery, chemotherapy, and radiotherapy. Even with such aggressive treatments, the survival for patient with GBM is only around one year. In that context, boron neutron capture therapy (BNCT) has emerged as a novel therapeutic strategy that selectively destroys tumors by the accumulation of 10B through a thermal neutron capture reaction to yield high linear transfer (LET) α particles and recoiling 7Li particles. These ionizing particles have high biological effectiveness and a short length which is approximately the size of tumor cells, leading to severe DNA damage and cell killing. Clinical trial for BNCT has demonstrated acceptable safety and prolonged survival on recurrent GBM patients, but the potential factor that could associated with the therapeutic effect of BNCT on patients with GBM is rare understand. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population consisting of monocytic (M-MDSC) and granulocytic (G-MDSC) subsets exerting immune suppression by damping the function of cytotoxic T lymphocytes and natural killer cells. In this study, we recruited 14 patients with life-threatening, end stage GBM. Their circulating MDSCs level was evaluated by flowcytometry before BNCT treatment. The results showed the level of circulating M-MDSCs almost mimicked the distribution of the absolute number. The average percentage of circulating M-MDSC was used as a cut-off value. Surprisingly, when the patient's pre-treatment level of circulating M-MDSCs was less than 5%, there will be almost a significant treatment effect, achieving complete response (CR) and partial response (PR) and elongation of PFS and OS. When the pre-treatment level of circulating M-MDSC was higher than 5%, the prognosis was progression disease (PD). Although the level of M-MDSCs was associated with the prognosis of clinical GBM patients, but the value does not correlate with tumor size. This study showed that the level of circulating M-MDSCs before treatment are prognostic to predict the treatment efficacy of BNCT in GBM patients, but further experiments are required to demonstrate the pathological response after successful BNCT and find the level of M-MDSC in circulation in relation to overall survival and progression free survival.

Keywords: GBM, BNCT, MDSC, high LET,

S1P2

Discrimination of gamma/neutron dose components by direct use of the ion collection efficiency curve.

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Introduction:
Knowledge of the linear energy transfer (LET) dose distribution of an unknown mixed (gamma + neutron) radiation field is required for both radiation protection and research. An example of a dose distribution discrimination technique is the dual chamber method. The method perfectly separates the low (gamma) and high (neutron) LET dose components, but the disadvantages of this method include: difficulty in determining the measurement point or non-simultaneous measurement of the low and high LET components. The topic of this presentation is a new method based on local ion recombination, which allows measurement in near real time at a well-defined measurement point. The method of separating the gamma and neutron components is particularly useful in Boron Neutron Capture Therapy research, where knowledge of the composition of the research or therapeutic beam is the basic input information for experiments.
Methods:
The recombination ionization chamber is a gas detector designed to provide local (as opposed to volumetric) recombination for a bias voltage below saturation. The intensity of this type of recombination depends on the local ionization density of the incident radiation and hence on the LET. The relationship between the local recombination intensity and the local ionization density is related to the charge drift time in the active region. The higher the voltage applied to the electrodes, the shorter the coexistence time of ions of opposite sign. This fact suggests that the current-voltage relationship (ion collection efficiency curve) of the detector is a distribution function of a certain probability distribution of the occurrence of particles characterized by the local ionization density. Based on these assumptions, a method has been proposed that allows the separation of high and low LET components based on the division of the ion collection efficiency curve into two interpenetrating parts corresponding to these compartments. By measuring 3 voltage points, it is possible to determine the fraction of high and low LET components of the mixed radiation field.
Results:
A series of measurements were performed for mixed radiation fields of 239PuBe + 60Co with different contributions of gamma and neutron components to the total dose. The results obtained with the developed method and the twin chamber method were compared. A very high agreement was obtained, for 10 different gamma/neutron proportions, the value at each measurement point was consistent with an accuracy of 2%. The measurement time for a single point was about 30 s. Conclusion The developed method gives very good results. Further work is needed to determine the applicability of the method. At this point, the method seems very promising for very broad applications. Recombination methods of dosimetry show a strong correlation with biological effects at the cellular level. A fast method for the separation of gamma/neutron dose components based on the recombination of ions in a gas at a well-defined geometric point could be very useful in research on BNCT therapy, among others.

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Keywords: BNCT, neutron dosimetry, mixed radiation

S1P3

Radiation safety survey and assessment of the Xiamen Humanity Hospital-Neuboron BNCT Center

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The Xiamen Humanity Hospital-Neuboron BNCT Center (XHH BNCT Center) stands as the first AB-BNCT clinical and research facility in China, incorporating the AB-BNCT system designed and developed by Neuboron Medical Group. In its initial phase, the center conducted comprehensive radiation safety assessments under beam parameters of 2.3 MeV and 8 mA, demonstrating robust radiation safety. At present, the beam has been stably operating at 2.35 MeV and 10 mA, we have extended our evaluations to ensure the continued radiation safety of the facility. Our assessments focused on three key areas: potential radiation exposure risks to staff, the public, and the environment. This involved:
1. Ambient Dose Equivalent Rates: With a proton energy of 2.35 MeV and a current of 10 mA impacting the lithium target, we measured ambient dose equivalent rates outside the controlled area, particularly in locations where staff might be exposed. Our findings showed that the ambient dose equivalent rates on the exterior of the shielding wall were roughly equivalent to environmental background radiation levels. Measurements near shielding doors, ventilation, and pressure relief holes revealed slightly elevated rates, but still below 2.5 μSv/h.These results deviation does not exceed 10% compared to the 8 mA beam current.
2. Residual Radiation: We mapped the distribution and temporal decay of residual radiation in the treatment room, including patient areas and staff positioning zones. This data allowed us to estimate the annual effective dose received by medical professionals working in these areas. According to the TLD monitoring results (2023.01 ~ 2023.11), the annual effective dose accumulated by the wearer did not exceed 0.6 mSv during the beam condition and preclinical research phase of this year.
3. Neutron-Induced Activation: We utilized an HPGe gamma-ray spectrometer to evaluate residual activation in the core area from prolonged neutron irradiation. The results indicated that the count rate of gamma peak is 0.3 cps at 1332 keV from cobalt-60, which is much lower than 2.1 cps at 1460 keV from natural radioactivity potassium-40.
4. Radioactivity of Used Li Targets: Addressing the handling of radioactive Li targets, we developed a semi-automatic target replacement device, minimizing radiation exposure to operators (below 6 μSv per replacement). Additionally, the design of the target storage box effectively reduced the surface dose rate to less than 10 μSv/h. In conclusion, our extensive surveys and measurements affirm the effectiveness of the radiation safety measures implemented at the XHH-BNCT Center. We will provide further details and comprehensive findings in the upcoming presentation.

Keywords: Safety Assessment, Residual Radiation, Shielding

S1P4

Antibody boron conjugate with a payload comprised of carborane-modified poly-L-lysine is capable of delivering boron to EGFR-expressing tumor cells

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Despite significant hurdles of the past, BNCT cancer treatment modality is gradually taking shape propelled by the regulatory approval of L-BPA in Japan for use in head and neck cancer and by the development of compact accelerators e.g. Neutron Therapeutics, Sumitomo and Alpha-Beam (TAE Life Sciences) capable of delivering tunable neutron beam in the epithermal range. At TAE Life Sciences, in addition to developing a modern neutron source, we strive to develop boron carriers for BNCT that could help overcome certain shortcomings of L-BPA, e.g. low solubility and the requirement for continuous infusion during treatment, and could potentially improve the outcomes of treatment by delivering higher boron content to cancer cells. We are also testing novel boronated antibodies. EGFR is expressed in a variety of H&N, breast and lung cancers. Thus, anti-EGFR antibody boron conjugates or ABC, could also become a therapeutic tool for targeted boron delivery, if unique challenges of appending multiple hydrophobic boron clusters through chemical ligation and generating a biological product with desirable pharmacokinetic and biodistribution following an i.v. administration could be solved. We synthesized a random benzaldehyde-activated poly-lysine-based polymer that was then conjugated site-specifically to an anti-EGFR mAb through engineered cysteins. This ABC-precursor was purified using ceramic hydroxyapatite column to remove both unconjugated polymer and high molecular weight-aggregated mAb. Carborane boron-enriched linkers were ligated to the polymer-mAb intermediate through oxyamine-benzaldehyde chemistry forming an ABC with approximately 200 borons. The product was then purified by desalting and characterized by ICP OES, size-exclusion analytical HPLC, binding affinity and an in-vitro boron uptake assay to show that the ABC is capable of delivering boron to the EGFR-positive cells. Boron uptake in the MDA-MD-468 tumor cells (60-70 µg/mg cell protein) was higher than in FaDu cell line and the difference in boron accumulation was in line with the difference in the EGFR copy number in these cell lines. Additional studies using tumor xenograft models in vivo are planned. We will present these findings as well as the bioconjugation process.

Keywords: EGFR, antibody-boron conjugate, carborane, FaDu

S1P5

Cobaltabis (dicarbollide) (COSAN) loaded APOFERRITIN: An innovative high-capacity boron delivery system to target tumour cells for BNCT applications.

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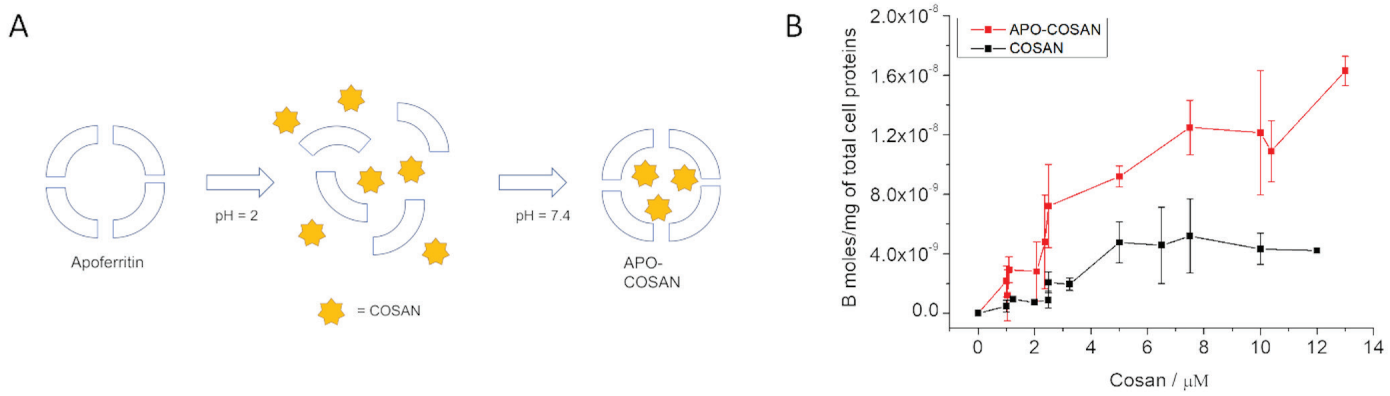

Figure captions:
Figure 1. a) Schematic representation of APO-COSAN loading method; b) Boron uptake by MCF7 cells with COSAN or APO-COSAN at different concentrations, 6h incubation, measured by ICP-MS.

One of the most significant challenges in achieving the great potential of BNCT is the development of highly targeted, effective, non-toxic, and biodegradable boron delivery systems. One promising strategy for reaching this aim involves the use of proteins. These macromolecules are excellent for the designing of drug delivery platforms because of their biocompatibility and the overexpression of their receptors and transporters on cancer cells. Ferritin is a 12 nm spherical protein consisting of 24 heavy (H)- and/or light (L)-chain peptide subunits arranged in a cage architecture with an 8 nm interior cavity used to store up to 4500 iron atoms. Upon removal of iron, the hollow spherical core of ferritin (named apoferritin) becomes available for loading a variety of cargo, including other metal ions, complexes, and biologically active substances, within its internal cavity, with potential applications in various biomedical fields.[1,2] This study suggests using Horse Spleen apoferritin (rich in L-chains) to deliver cobaltabis(dicarbollide) (COSAN) selectively to MCF7 human breast cancer cells by exploiting the ability of this protein to target SCARA-5 receptors overexpressed on MCF7 tumours. [3] There are numerous benefits related to employing COSAN [4]: 1) high boron content (18 atoms/molecule), 2) membrane-crossing capability, and 3) a negligible effect on the viability of cells. Employing a highly effective encapsulating strategy, which disaggregates the apoferritin nanostructure in an acidic environment (pH=2) and subsequently reassembling it under physiological pH conditions (7.4), a remarkably high cargo loading capacity was achieved. Specifically, 7.5 ± 3.5 COSAN molecules or 135 boron atoms were efficiently encapsulated within the apoferritin internal cavity, highlighting the exceptional cargo-loading potential of this protein nanocage.
Next, using ICP-MS, the boron uptake by MCF7 cells was evaluated and the results were compared to those obtained upon incubation with COSAN alone at the same concentrations. When cells were incubated with APO-COSAN, they internalized about 3 times more boron with respect to cells only exposed to COSAN. In summary, apoferritin is a highly effective and targeted delivery vehicle for boron containing compounds; moreover, imaging agents for biodistribution monitoring can be accommodated in the protein cavity. BNCT will be used to assess the cytotoxic effect attained following neutron irradiation on cells incubated with COSAN and APO-COSAN.

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[4] Fuentes I et al Chem. Eur. J, 24, 17239, 2018. Keywords: COSAN, apoferritin, breast cancer, nanoparticles

S1P6

Develop Boron-Containing Drugs and Boron Cluster in Organic Synthesis

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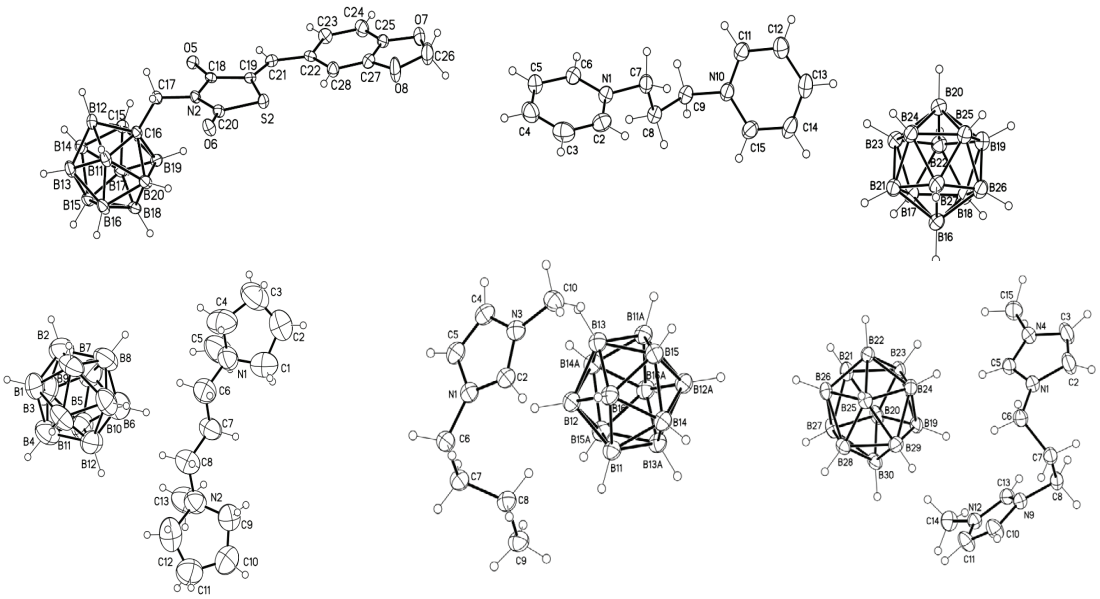

Figure captions: The X ray structure of carborane-base compounds.

My research team effort on development boron containing drugs and boron relative chemistry, in this research, we present new class of analogs of leucettamine B. The 25 newly synthesized compounds were tested for anticancer activity. Among them, the carborane-based compound (Z)-5-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(1-closo-carboranyl)-2-thioxo -thiazolidin-4-one shown potential derivatives against tumor cells. The carborane derivative has the lowest IC_{50} value against the SW480 cell line (4.7 μM) and Mahlavu (6.6 μM) cell line. Our research shows that leucettamine B analogs might have the potential in cancer chemotherapy. [1] We also develop carboranes-based ligands for catalysts, we can utilize the excellent metal chelation properties and the stereochemical properties of carboranes to develop their catalytic activity and further expand their applications in organic synthesis. Carboranes are less explored for their role as a ligand in carbon-heteroatom bond formation reactions. Herein we disclosed our results on carbon-nitrogen bond formation by treating N-heterocycles with aryl halides in the presence of a copper catalyst and carborane diamine ligand. This methodology will establish new chemical space to explore among the scientific community. In conclusion, new ligand nido-carborane diamine has been established for the Ullmann type C-N coupling reaction between N-heterocycles and aryl halides. The reaction was found to be adaptable for a wide range of substrates. Aryl halides carrying either bromo or less reative chloro group was tolerable with good to high yields. Many different N-heterocycles were utilized under the newly developed conditions. More applications of these interesting bulky boron clusters are underway in our laboratory and will be reported in due course. Furthermore, we also synthesize and characterize several new dodecarborate ionic liquids. We synthesized a range of carborane Schiff bases using 1-aminocarborane and 1-formylcarbaborane as the building blocks. These compounds are expected to serve as ligands in organic reactions, enabling catalytic processes. Alternatively, they can be utilized as novel catalysts after metal complexation.

References: 1. Bioorganic Chemistry 2020, 98, 103729.

Keywords: BNCT, Boron-Containing Drugs, Boron Cluster

S1P7

Evaluation of the distribution of BPA in a rat brain tumor model using matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) in comparison with liquid chromatography/tandem mass spectrometry (LC/MS/MS)

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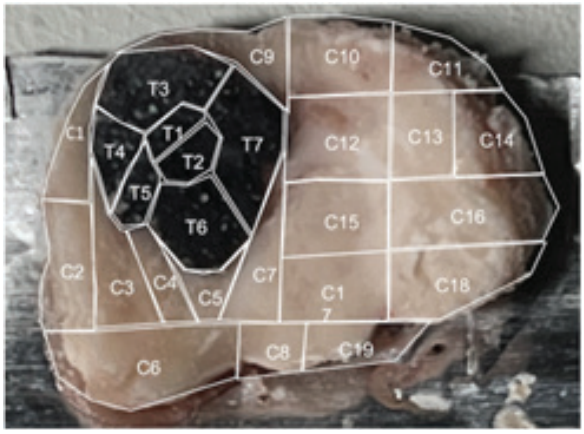

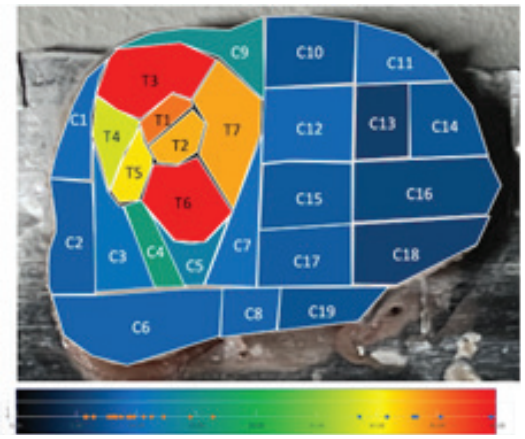

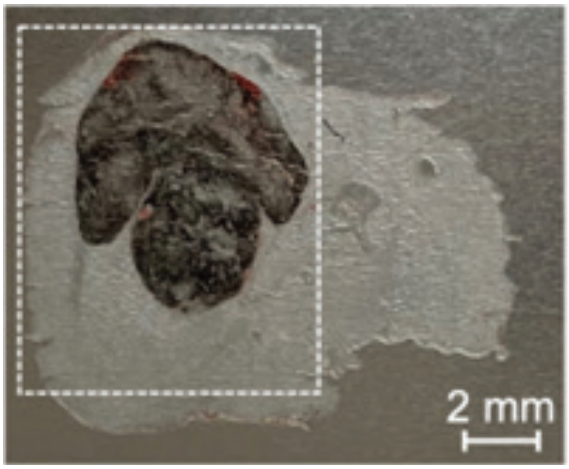

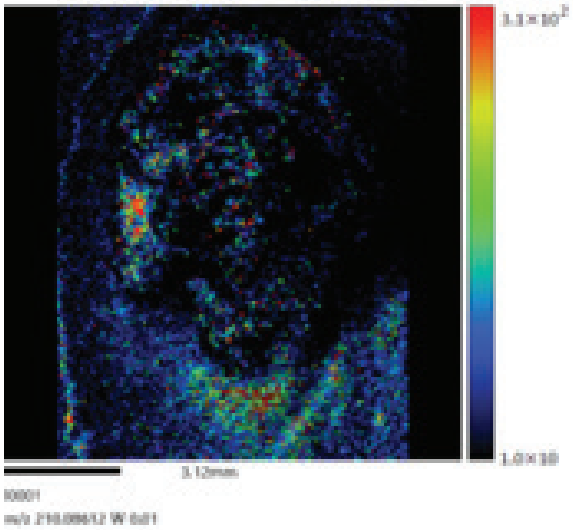

Table 1. Comparison of T/N ratio estimated via MALDI-MSI and LC/MS/MS

Sample No.	MALDI-MSI T/N [a]	LC/MS/MS T/N [a]	Relative ratio MALDI and LC/MS/MS
T3	2.4 (%RSD 28, n=3)	5.0	0.48
T6	2.3 (%RSD 31, n=3)	5.0	0.45

[a] The value of the C2 segment was used as the value of normal tissue (N). The T/N ratios obtained using MALDI-MSI were calculated as intensity ratios of $[BPA+H]^+$ on the pixel-averaged mass spectra. The pixel-averaged mass spectra were obtained from the ROIs (n=3) of T3 and T6.

Figure captions:
Figure 1. (a) Brain sample segments of rat melanoma model and (b) boron distribution mapping.
Figure 2. (a) Thin brain section and (b) Ion image of [BPA+H]+ at m/z 210.086.

[Introduction]
The range of alpha and lithium particles emitted by BNCT based on ^{10}B (n,α)^{7}Li reaction is within 10 μm. Thus, the therapeutic effects of BNCT depends on the distribution of boron at the μm order. Therefore, for basic research, it is crucial to use technology that has high spatial resolution and is capable of determining the spatial distribution of boron within the tissue sample, including in both tumor and normal cells. Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging (MSI) has the advantages of simultaneous detection of multiple organic compounds and high sensitivity without the need for derivatization. In our previous study, we applied MALDI-MSI on tissue section of rat brain tumor model in order to visualize the distribution of 4-borono-L-phenylalanine (BPA) with dimensions of approximately 10 mm on each side, at a spatial resolution of 60 μm [1]. However, the response obtained in each pixel may not solely represent the abundance of BPA in the ion images obtained from MALDI-MSI. Therefore, the mass spectral intensity of BPA obtained via MALDI-MSI, in both tumor and normal tissues, should be evaluated using quantitative methods. In this study, we use a rat brain tumor model to compare the distributions of BPA in brain tissues, as obtained from MALDI-MSI and liquid chromatography/tandem mass spectrometry (LC/MS/MS), in order to demonstrate the feasibility of a method for evaluating the distribution of BPA using images obtained via MALDI-MSI.

[Materials and methods]
We prepared a rat brain tumor model (melanoma) and administered BPA intravenously. A BPA-dosed brain sample was divided into two parts along with the center of the tumor. A brain segment was excised into thin slices using a cryostat microtome and subjected to MALDI-MSI to obtain a mass spectrometry image (defined as an ion image) of BPA. The other segment was divided into several parts, and BPA was extracted from each part in order to quantify the BPA via LC/MS/MS.

[Results]
LC/MS/MS measurements were performed for 7 segments of tumor tissue (T1-T7) and 19 segments of normal cerebral cortex tissue (C1-C19) of a brain from the rat administered with BPA, as shown in Fig. 1a. Fig. 1b shows the heat map of boron distribution obtained from LC/MS/MS. The boron concentrations in the T3 and T6 segments were significantly higher than those in other tumor segments, indicating differences. The boron concentrations in C4, C5, and C9 segments, adjacent to the tumor, were higher than in other segments of normal tissue further away from the tumor. On the other hand, a photographic image of a brain section for MALDI-MSI and an ion image of the protonated BPA molecule $[BPA+H]^+$ at m/z 210.086, generated in the 0.01 Da mass window, are shown in Fig. 2a,b. The ion image of $[BPA+H]^+$ shows similar distribution with the boron distribution mapping obtained via LC/MS/MS, shown in Fig. 1b. In particular, T3, T6, C4, and C5, shown in Fig. 1b, exhibit high concentrations of BPA, with high intensities also seen in the corresponding regions in Fig. 2b. T/N ratio in MALDI-MSI were 2.4 for T3 and 2.3 for T6 as listed in Table 1. We defined the ratio of T/N ratios obtained from MALDI-MSI and LC/MS/MS as the relative T/N ratio. The consistent relative T/N ratios in T3 and T6 regions were obtained (0.48, 0.45).
[Conclusion]
The distribution based on the ion image of $[BPA+H]^+$ obtained from MALDI-MSI was similar to the results of boron distribution mapping obtained from LC/MS/MS. The consistent relative T/N ratios obtained from MALDI-MSI and LC/MS/MS suggest the possibility for MALDI-MSI to enable the estimation of T/N ratios by correcting it using the boron concentration determined by LC/MS/MS.

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Keywords: BNCT, MALDI-MSI, LC/MS, BPA, brain

S1P8

Development of novel small molecule boron carriers targeting the amino acid transporter ASCT2

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Boronophenylalanine (BPA) is a boron agent with a structure similar to phenylalanine that accumulates in cancer cells via L-type amino acid transporter 1 (LAT1). The world's first accelerator-based BNCT insurance treatment for head and neck cancers using BPA was approved by the Japan Pharmaceuticals and Medical Devices Agency in 2020. However, there are still many cancer cell types with low expression of LAT1 and insufficient accumulation of BPA. Therefore, novel boron agents that are taken up by cancer cells through a mechanism different from BPA are required to expand the indications for BNCT. We focused on the alanine serine cysteine transporter 2 (ASCT2), a Na^+-dependent neutral amino acid transporter, as a novel mechanism for boron delivery to target tumor cells. Typically, ASCT2 transports substrates such as alanine, cysteine, asparagine, serine, and threonine. In the acidic environment characteristic of tumor tissue, ASCT2 plays a role in facilitating the uptake of glutamic acid into cancer cells. Furthermore, it has been reported that various types of cancer cells express ASCT2 more prominently than normal cells[1]. In this study, we developed novel boron compounds that can be internalized into cancer cells via the ASCT2 pathway. Initially, we designed GluB-1, a boron compound mimicking the structure of glutamic acid, a substrate for ASCT2 transport. In this design, we replaced the carboxy group in the glutamic acid side chain with a boric acid group. To mitigate potential neurotoxic effects associated with high doses of glutamate[2], we introduced a carbon chain into GluB-1, aiming to minimize neurotoxicity while preserving the ASCT2-mediated uptake mechanism. Additionally, we also formulated GluB-2 with an extended carbon chain and GluB-3 with two carbon chain lengths. The large-scale synthesis of these GluBs was achieved using amino acid derivatives as starting materials, followed by the incorporation of boric acid groups. Subsequently, we evaluated the cytotoxicity and cellular uptake of GluBs at the cellular level. The results demonstrated that GluBs exhibit high water solubility without additives, showcased low cytotoxicity, and displayed intracellular uptake comparable to that of BPA. Moreover, the ASCT2 inhibitor V9302[3] partially impeded this uptake, suggesting an alternative cellular uptake mechanism beyond ASCT2. We investigated the in vivo boron distribution of GluBs using a colon cancer-transplanted mouse model. Consequently, GluB-2 exhibited significant tumor accumulation compared to BPA, with a maximum tumor boron concentration reaching 30 μgB/g, surpassing clinically desirable values[4]. Finally, we assessed the anti-tumor effect of GluB-2 in BNCT using a colon cancer-transplanted mouse model. The results showed that tumor regression was observed in all mice treated with GluB-2, indicating that GluB-2 is a promising next-generation boron drug to complement BPA.

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Keywords: ASCT2,Glutamic acid mimicking compounds,BNCT effect

S1P9

Boron Nitride Quantum Dots as multifunctional nanomaterials for Boron Neutron Capture Therapy

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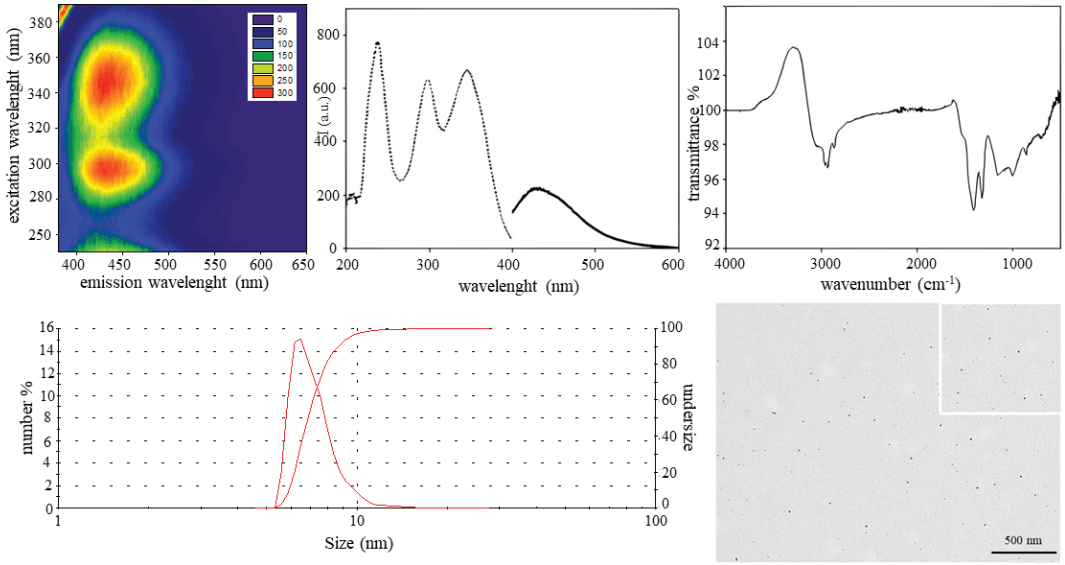

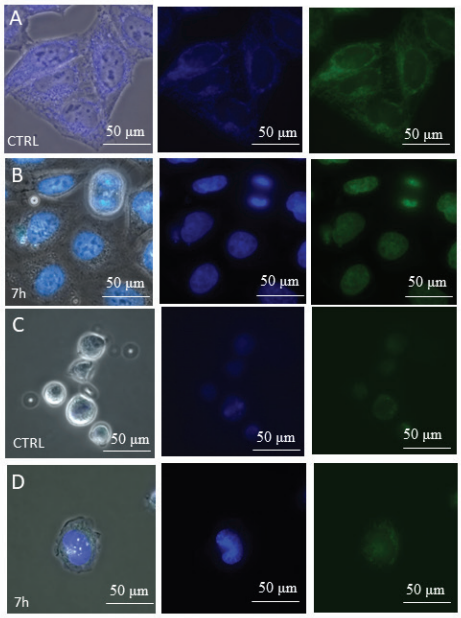

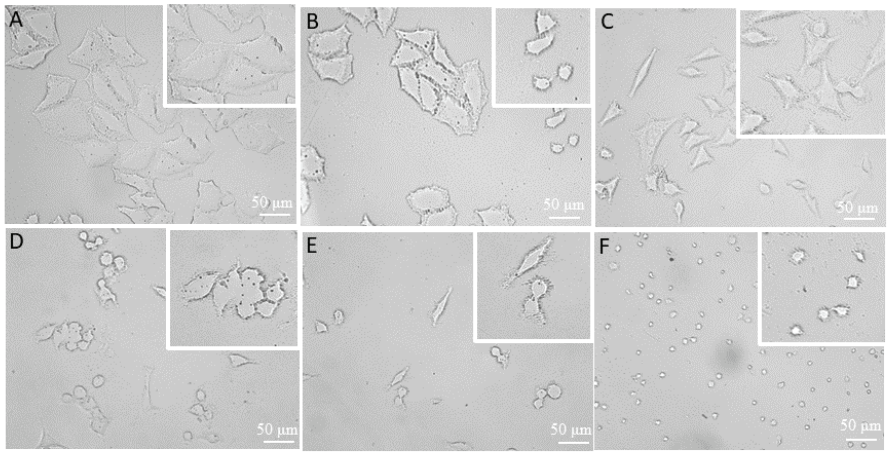

Figure captions:
Figure 1. Characterization of BNQDs, in terms of optical properties and size
Figure 2. Confocal microscopy images of both HeLa and Jurkat cells incubated with BNQDs
Figure 3. Neutron autoradiography

Nanoparticles of inorganic boron-containing compounds show great promise as carriers of ^{10}B for Boron Neutron Capture Therapy (BNCT). This study is dedicated to the synthesis, characterization, and evaluation of the biological activity of Boron Nitride Quantum Dots (BNQDs). BNQDs, recognized for their unique electronic and optical properties, have become a captivating class of nanomaterials with diverse applications. Due to their biocompatibility and low toxicity, they have been previously explored in biomedical applications such as bioimaging and drug delivery.[1,2] Boron Nitride, with its high volumetric boron content, allows for a significant accumulation of boron in tissues, eliminating the need for isotopically enriched compounds. Furthermore, BNQDs possess intrinsic fluorescence, serving a dual purpose as ^{10}B carriers and bioimaging tools. The photoluminescent properties of BNQDs arise from a synergic interplay of various defects in their structure. These defects include carbene-like edges, nitrogen or boron vacancies, the substitution of nitrogen atoms with carbon (C) atoms, the presence of 1,3-B centres, and the occurrence of species like BO^-_2 [3]. In our methodology water suspensions of BNQDs were synthesized through a hydrothermal process, and their interaction with biological systems was examined using two different cell lines: HeLa cells and Jurkat cells. Following an investigation into their cytotoxicity, the internalization of BNQDs in both cell lines was assessed through confocal microscopy and neutron autoradiography. After few hours of incubation, both HeLa and Jurkat cells present a strong blue luminescence when the sample is irradiated in the DAPI range (340-380 nm). This fluorescence is strictly localized in the cells nuclei and is not present in control samples (Figure 2). Moreover, when applying a filter for the blue fluorescence, the cell nuclei still emitted in the green region, due to the wide emission band of BNQDs. Prolonging the incubation time of HeLa cells with BNQDs up to 14 h, showed that the cells nuclei were no longer stained and bright luminescent spots can be observed in the perinuclear region. Similar results were obtained with Jurkat cells, suggesting that BNQDs are slowly transferred from the nuclei to the cytoplasm, but confirming their presence in cells for up to 24 hours without cell viability being affected. The presence of internalized BNQDs has been confirmed by intracellular neutron autoradiography. This analysis evidenced that samples of both cell lines incubated with BNQDs for 7h, presented tracks in the cells' nuclei. After 7 hours of incubation, 75% of HeLa cells resulted positive to the presence of ^{10}B in their nuclei. As for Jurkat cells, 61% of the cells presented tracks. Micro-distribution studies provided valuable insights into the spatial distribution of BNQDs within single cells and the overall cell population. These findings strongly suggest that BNQDs hold significant promise as multifunctional ^{10}B carriers for Boron Neutron Capture Therapy.

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Keywords: BN, quantum dots, BNCT

S1P10

Development of novel [18F] FBPA synthesis method using automatic synthesizer and quality control methods.

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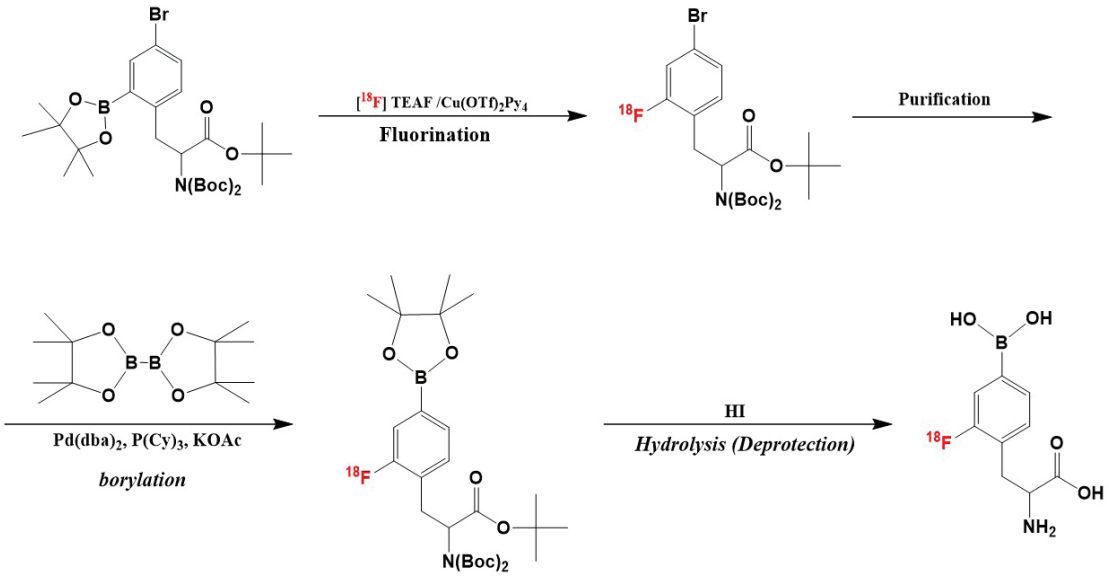

Figure captions:
Figure 1. figure of modified type of MPS-200 Aβ
Scheme 1. Synthesis rote of [18F]FBPA

Objectives: 2-[^{18}F]Fluoro-4-borono-phenylalanine (FBPA) is an important PET tracer for the determination of Boron Neutron Capture Therapy (BNCT) applicability. Nowadays [^{18}F]FBPA is mostly produced from [^{18}F]F_2 gas. We previously reported a novel [^{18}F]FBPA synthesis methods from [^{18}F]HF which is produced by ^{18}O(p, n)^{18}F nuclear reaction. While, a nuclear reactor was formerly needed for a neutron source in BNCT. A cyclotron neutron generation system was recently established. Due to this change, BNCT has possibility to expanding all over the world. As BNCT expands, we need more [^{18}F]FBPA radioactivity in one synthesis. Since [^{18}F]F^- yield of ^{18}O(p, n)^{18}F nuclear reaction is larger than that of ^{20}Ne (d, α)^{18}F reaction. We previously reported a novel [^{18}F]FBPA synthesis from [^{18}F]F^- which is produced by ^{18}O(p, n)^{18}F nuclear reaction. In this study, we tried to adopt this method for automatic synthesizer for clinical use.

Methods: We used a modified type of MPS-200 Aβ (Sumitomo Heavy Industry, Tokyo, Figure 1) as the automatic synthesizer. The synthesis scheme is shown in Scheme 1. The first step is ^{18}F-fluorination in the first reaction vessel. In this step, 7 mg of pinacol borane precursor and 20 mg of copper reagent ($Cu(OTf)_2(py)_4$) were used for [^{18}F]fluorination step in first reaction vessel. The reaction condition consists of 80-degree reaction temperature and 20 min reaction time in a mixture of n-butanol (n-BuOH) and dimethyl acetamide (DMA) mixture (1/2 v/v). After the fluorination reaction, the reaction solution was passed through silica gel (SH silica) cartridge column to remove the copper reagent and transferred to second reaction vessel. In the borylation step, we used 40 mg of bis (pinacolato)diboron, 6.0 mg of bis(dibenzylidene acetone)palladium(0), 6.0 mg of tricyclohexyl phosphine and 5.0 mg of potassium acetate in dimethy formamide (DMF). The reaction temperature was 110-degree and the reaction time was 20 min. Then, the reaction solution was passed through a tC18 cartridge column to remove an Insoluble and by-product materials. Purified reaction mixture was moved to third reaction vessel. Hydroiodic acid was added to reaction mixture for deprotection. The reaction condition of this step was 100 degree in reaction temparature and reaction time was 5 min. A crude mixture was purified by HPLC (High Performance Liquid Chromatography). Finally, [^{18}F] FBPA fraction was collected after HPLC purification of the crude mixture. Radiochemical purity (RCP) and molar activity (MA) were determined by HPLC. The concentrations of n-BuOH, DMA and DMF were measured with gas chromatography.

Result: Reaction efficiencies determined by HPLC and TLC (Thin-Layer Chromatography) in fluorination, bolylation and deprptection (hydrolysis) step were 85 %, 80 % and 88 %, respectively. The radiochemical yield of [^{18}F]FBPA from [^{18}F]HF was more than 10% (non-decay collected). Total synthesis time from the end of bombardment was about 110 min. RCP and MA of [^{18}F]FBPA were more than 90% and 1,000 GBq/μmol, respectively. Each concentration of n-BuOH, DMA and DMF was less than 100 ppm. About 9 GBq of [^{18}F]FBPA was produced by our method with 60 min and 50 microA irradiation using 12 MeV cyclotron.

Conclusion: We succeeded in synthesizing [^{18}F]FBPA from [^{18}F]HF using an automatic synthesizer that can be used in clinical situations.

Keywords: FBPA, PET, BNCT

S1P11

Development of novel low-molecular boron carriers targeting biotin receptors for BNCT

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In 2020, accelerator-based BNCT for head and neck cancers using 4-borono-L-phenylalanine (L-BPA) was approved by the Pharmaceuticals and Medical Devices Agency in Japan, making BNCT a more accessible treatment. L-BPA is actively transported into tumor cells thorough L-type amino acid transporter 1 (LAT-1). However, LAT-1 is not highly expressed in all types of cancers. Hence, there is an urgent need to develop boron carriers with novel tumor-uptake mechanisms to expand the range of BNCT applications. We focused on biotin as a targeting unit specific to cancer cells. Typically, biotin is a vital vitamin essential for the division of all cells, particularly crucial for the growth of tumor cells. Furthermore, it has been reported that biotin receptors (BRs) are overexpressed in various types of cancer cells[1]. Among BRs, the Sodium-Dependent Multivitamin Transporter (SMVT) is presumed to be involved in biotin uptake and is considered a potentially useful cancer biomarker for tumor diagnosis. Recently, a biotin-modified MRI/Gd BNCT theranostic contrast agent was reported; however, the boron source used was a poorly water-soluble carborane[2]. Boron carriers targeting BRs with low toxicity, water solubility, and biocompatibility, have not yet been developed. In this study, we endeavored to develop a novel low-molecular boron carrier capable of internalizing into cancer cells via the BR pathway.
Initially, we designed a biotin-closo-dodecaborate conjugate (BBC) and also biotin-closo-dodecaborate conjugated with a 4-(p-iodophenyl)butyric acid moiety (BBC-IP) binding to albumin that accumulates into tumors due to enhanced permeability and retention (EPR) effect. We achieved the synthesis of BBC by condensing biotin with an ionic boron cluster, followed by exchanging its counter-cation from a quaternary ammonium salt to a sodium salt to make the cluster water-soluble. For the synthesis of BBC-IP, we initially conjugated the iodophenyl group, boron cluster quaternary ammonium salt, and biotin onto a lysine scaffold based on our previous design of boron carriers targeting a folate receptor[3]. We then replaced the counter-cation of the boron cluster with sodium and remove impurities through a washing process. In general, low molecules containing biotin often face challenges in water solubility, but both BBC and BBC-IP exhibited high water solubility without the need for additives. We will also report on the in vitro and in vivo evaluation of BBC and BBC-IP as boron drug candidates for BNCT.
We anticipate that BBC-IP based BNCT could provide an alternative approach for treating tumors resistant to L-BPA based BNCT.

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Keywords: boron cluster, biotin, albumin

S1P12

Development of boron drug for BNCT targeting glucose transporter

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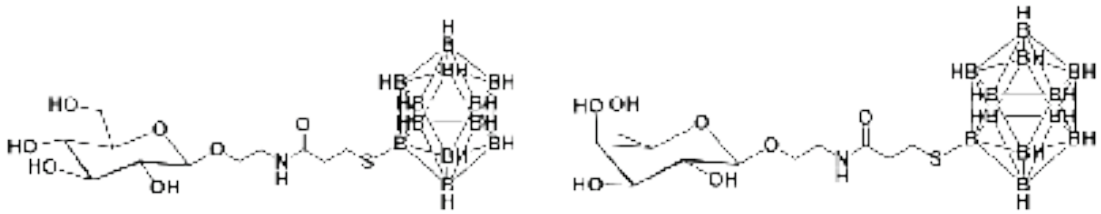

Fig.1) Structural formula of Glycoconjugate-BSH

Figure captions: Structural formula of Glycoconjugate-BSH

INTRODUCTION

BPA, the only approved drug for BNCT in Japan, has shown excellent therapeutic efficacy in clinical practice. However, its therapeutic mechanism is due to its intracellular uptake via amino acid transporter (LAT-1). Therefore, other strategies are needed when targeting tumor cells that do not express high levels of LAT-1 [1-3]. Therefore, we designed a drug (Glycoconjugate-BSH) targeting Glucose transporter (GLUT-1) by chemically binding BSH (Borocaptate sodium), which has been clinically applied in the past, to sugar [4]. As we aim to expand the indications for BNCT in the future, it is significant to study boron delivery using transporters other than LAT-1.

MATERIAL AND METHODS

Glycoconjugate-BSH was exposed to Chinese hamster lung-derived fibroblasts (V79 379A) and cytotoxicity was evaluated by WST assay. Glycoconjugate-BSH was also exposed to mouse colon cancer cells (CT26) and each tumor cell and compared for intracellular translocation. The amount of intracellular translocation was confirmed by measuring the concentration of boron by radiofrequency inductively coupled plasma atomic emission spectrometry (ICP-AES). Furthermore, each tumor cell exposed to Glycoconjugate-BSH was irradiated with neutron beams to confirm the cell killing effect by colony formation assay.

RESULTS AND DISCUSSION

As Glycoconjugate-BSH, we investigated the introduction of BSH into glucose using Michael addition reaction. Glucose-BSH was successfully synthesized by using NaOH to introduce BSH into a derivative of glucose with N-(2-hydroxyethyl)acrylamide at the 1-position of glucose. Similarly, Galactose-BSH, which is BSH introduced into galactose, was successfully synthesized. In vitro, the low toxicity of Glycoconjugate-BSH was confirmed. In addition, boron was detected in the cells by ICP, suggesting intracellular delivery of Glycoconjugate-BSH via GULT-1. In addition to these results, the cell-killing effect was obtained by neutron irradiation, suggesting that even carcinomas with low LAT-1 expression could be highly therapeutic with BNCT due to GLUT-1 expression. in vivo experiments will be conducted in the future for the development of Glycoconjugate-BSH.

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Keywords: Drug delivery system, Glucose transporter

S1P13

In vivo Efficacy and Dose Dependent Response of [10B]BPA Irradiation Therapy in SAS Tumor Bearing Athymic Nude Mice

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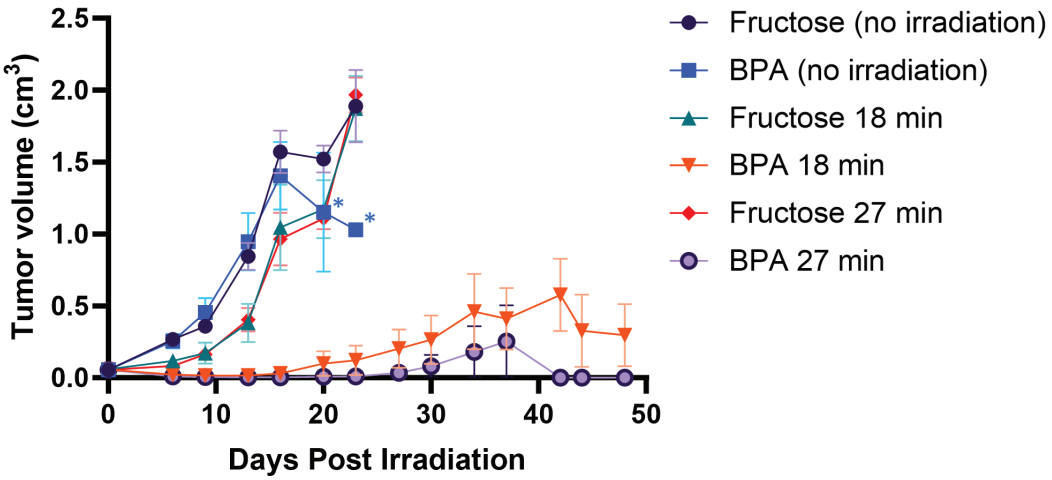

*Animal deaths due to reaching predetermined study end points account for lower tumor volume measured for remaining mice.

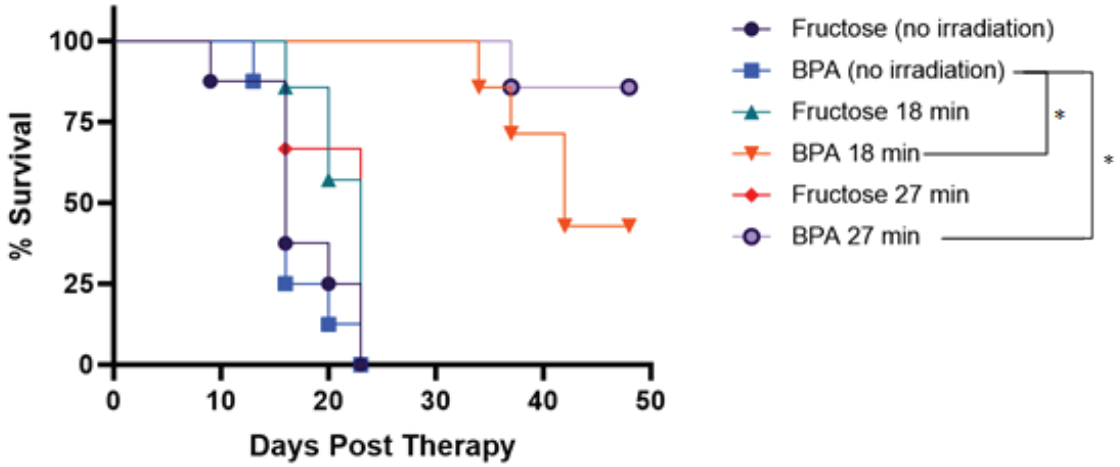

Figure captions:
Figure 1: Average tumor volumes by study group over time.
Figure 2: Survival curves following [10B]BPA neutron capture therapy.

Boron neutron capture therapy (BNCT) is an evolving area of cancer therapy in which [^{10}B] is selectively delivered to tumors cells, followed by neutron irradiation to produce high energy, low LET, ^{7}Li and alpha emissions.[1,2] [^{10}B]BPA has been studied in numerous phase I/II clinical trials.[3] As part of an ongoing collaboration between Aviko Radiopharmaceuticals, Inc. and University of Missouri-Columbia, we have investigated the in vivo efficacy of [^{10}B]BPA formulated in fructose in SAS tumor-bearing athymic nude-Fox1nu mice. Mice (n = 48) were implanted with SAS human tongue squamous cell xenografts. After 18 days of tumor growth, tumor measurements were taken, and animals were randomized into study groups. Animals received either 500 mg/kg [^{10}B]BPA or the equivalent (649 mg/kg) fructose dose via s.c. injection to the shoulder contralateral to the tumors.

One hour after dose administration mice were anesthetized with 50 µL of ketamine/xylazine (1.25 mg/0.125 mg) and irradiated using the thermal neutron beam at the University of Missouri Research Reactor (MURR) for either 18 min or for 27 min with a measured neutron flux of 8.8 x 10^8 n/cm^2s. Their cranial half was shielded using a $^6Li_2CO_2$ impregnated polyethylene irradiation gantry. [^{10}B]BPA and neutron therapy was well tolerated by the mice, however some mortality was noted that was likely related to injectable anesthesia. Tumor measurements, body weight and clinical condition were recorded twice weekly for the duration of the study. Post-irradiation, mice were sacrificed when predetermined study end points were met, including weight loss greater than or equal to 20% of initial weight, growth of tumor beyond 1 cm in longest dimension, bleeding or skin ulceration. The study was terminated 48 days post-treatment. SAS tumor growth data (Figure 1) shows the average tumor volumes for groups that received 500 mg/kg [^{10}B]BPA with irradiation decreased after treatment and remained small, growing at a much slower rate throughout the study than control groups that received no irradiation or groups that received neutron irradiation alone with a vehicle only dose of 649 mg/kg Fructose. A notable improvement in survival (Figure 2) was observed for 500 mg/kg [^{10}B]BPA treatment with irradiation compared to 500 mg/kg [^{10}B]BPA with no irradiation (P value < 0.0001 for both 18 min and 27 min) and when compared to irradiation alone with vehicle only dose of 649 mg/kg Fructose (P value = 0.0004 for 18 min irradiation, P value = 0.0006 for 27 min irradiation). A second objective of this study was to determine if there is a difference in efficacy based on irradiation dose. While there was a much better survival rate (86%) for the group that was irradiated for 27 min than the 18 min irradiation group (43% survival), the difference between these curves was not significant (P value = 0.12). Further studies may be needed to determine the minimum irradiation dose needed for therapeutic efficacy. These data confirm the expected efficacy of BPA for [^{10}B] delivery in conjunction with BNCT and establish a basic protocol for future screening of novel [^{10}B] drug candidates *in* vivo.

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Keywords: BNCT, borophenylalanine, preclinical studies

S1P14

HES-boron cluster conjugate as a potential boron delivery carrier in boron neutron capture therapy

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Boron Neutron Capture Therapy (BNCT) is a tumor-selective targeted radiotherapy, which may become a promising treatment method for patients with cancer located in hard-to-reach areas with limited treatment options. Despite the fact, that BNCT has been successively developed since 1950s, effective delivery of boron-rich compound in target tissues remains a significant challenge. For this reason, many efforts are being made to develop novel boron-rich compounds that will efficiently accumulate in the tumor tissue. The objective of this study was to design a macromolecular conjugate capable of facilitating the effective and selective transportation of boron atoms into cancer cells. The utilization of a boron-rich metallacarborane in conjunction with the well-established drug carrier, hydroxyethyl starch (HES), has resulted in the development of innovative nanoparticles. This was achieved through an unconventional mechanosynthesis approach. Hydroxyethyl starch is a polysaccharide derived from amylopectin, synthesized through the hydroxyethylation reaction involving waxy corn or potato starch and ethylene oxide in an alkaline solution. Characterized by a branched structure with (1,4) and (1,6)-glycosidic bonds, HES allows attachment of hydroxyethyl groups at the C2, C4, and C6 positions[1]. HES possesses favorable pharmacological properties, making it a valuable volume plasma expander when administered as a solution in medical practice[2]. Its attributes of nontoxicity, biocompatibility, and biodegradability further enable its utilization as a carrier for drug delivery of small agents. Notably, HES has been studied for its substitution with anticancer drugs such as methotrexate[3-5], doxorubicin[6], 5-fluorouracil[7], and 10-hydroxy camptothecin[8]. These investigations highlight HES as a promising agent for enhancing the pharmacodynamics and pharmacokinetics of well-established medications[1]. Metallacarboranes serve as versatile platforms extensively employed in the development of bioactive compounds with potential therapeutic applications[9]. Their distinctive cage-like structure allows for the strategic arrangement of substituents, facilitating the customization of molecular targets[10]. Additionally, metallacarboranes can cause favorable interactions with biomolecules through mechanisms such as hydrogen and dihydrogen bonding, hydrophobic interactions, and chaotropic effects[11]. In the field of metallacarboranes, cobalt bis(dicarbollide) (COSAN) stands out due to its exceptional properties. COSAN exhibits the ability to traverse cell membranes and accumulate intracellularly, including within the cell nucleus. Its 3D aromaticity and a single negative charge contribute to its remarkable thermal, chemical, and biological stability, distinguishing it as an exceptional abiotic compound[12]. These unique features stimulate advancements in drug design contributing to the growing popularity of COSAN in medicinal chemistry. COSAN is frequently employed in the synthesis of biologically active hybrid organic–inorganic derivatives which find application in boron neutron capture therapy (BNCT)[13,14]. The synthesis of HES-CoSAN conjugates was conducted in the Planetary Micro Mill PULVERISETTE 7 classic line rotary mill (Fritsch) equipped with 12 ml stainless steel grinding bowls and 5mm diameter balls. The conjugates were characterized for hydrodynamic size and zeta potential. In vitro studies allowed us to evaluate the amylase digestion rate, hemotoxic activity and cytotoxic activity against following mouse cell lines: RAW 264.7 macrophages, NIH/3T3 fibroblasts, TRAMP-C1 prostate cancer, and B16-F0 melanoma. The conjugates have been functionalized with folic acid to give them selective activity and allow for receptor-mediated cellular uptake in cancer cells with folate receptor overexpression. The obtained HES-boron cluster conjugates in its original form, as well as after functionalization with folic acid, did not show toxicity against tested normal and cancer mouse cell lines, even at high concentration. Thus, appropriate hydrodynamic parameters and particles containing a large number of boron atoms allowed for the creation of a boron carrier, which may contribute to the significant development of BNCT therapy.

The study was funded by National Science Center, Poland (Grant No. 2019/33/B/NZ5/02212).

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Keywords: BNCT, HES-boron cluster conjugate, metallacarborane

S1P15

Development of theranostic compounds with boron and gadolinium for combination neutron capture therapy with nuclear medicine imaging

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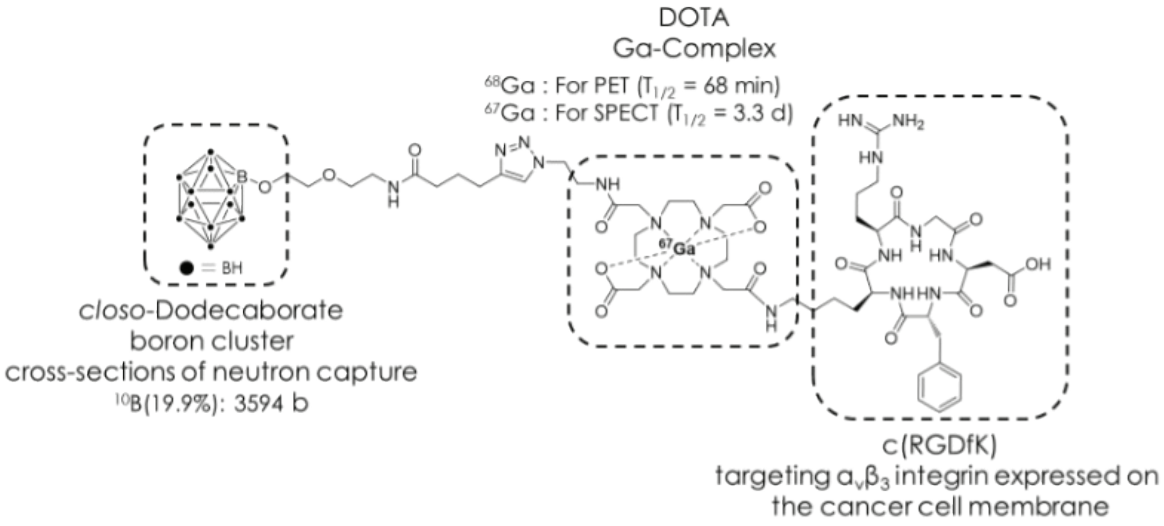

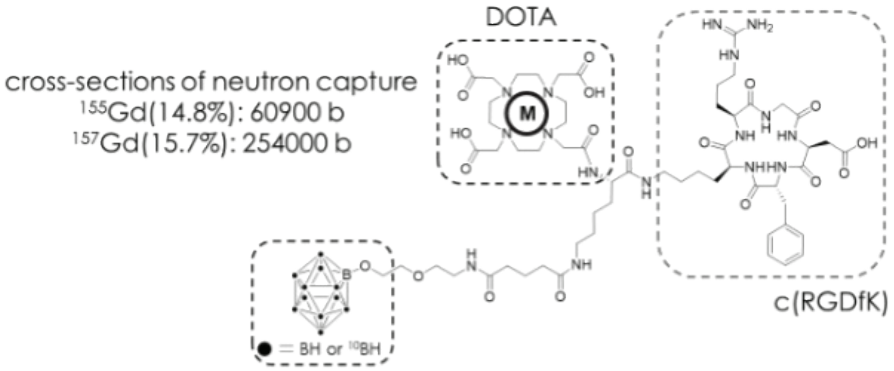

Figure captions:
Figure 1. Chemical structure of [Ga-67]1.
Figure 2. Chemical structure of (2: M = Ga) and (3: M = Gd).

Background: In boron neutron capture therapy, it is important to predict the biodistribution of boron compounds in advance. For this theranostic system, imaging probes and therapeutic boron compounds with the same chemical structure should be ideally used. Recently, our research group developed a probe, closo-dodecaborate-(Ga-DOTA)-c(RGDfK) (**1**) (Figure 1), containing closo-dodecaborate ($[B_{12}H_{12}]^{2-}$) as a boron cluster, a [^{68}Ga]GaDOTA as a stable ^{68}Ga complex for PET (Positron Emission Tomography) imaging, and an arginine–glycine–aspartic acid (RGD) peptide targeting $\alpha_v\beta_3$ integrin expressed on the cancer cell membrane[1].
Compound **1** showed high accumulation in tumors and low accumulation in non-target tissues. However, the synthesis method of **1** resulted in low yields and the radiolabeling time exceeding 6 h. Consequently, its application to ^{68}Ga ($T_{1/2}$: 68 min), which is more practical for clinical use, was not feasible.
In this study, closo-dodecaborate-K-[^{67}Ga](Ga-DOTA)-c(RGDfK) (**2**) (Figure 2), which can be coordinated with gallium in the final step, was synthesized. Moreover, the precursor could also coordinate with gadolinium as a heptacoodinated complex, in which ^{157}Gd has the largest cross-sections to capture thermal neutrons and is expected to be useful as an element for neutron capture therapy (NCT). Therefore, closo-dodecaborate-K-(Gd-DOTA)-c(RGDfK) (**3**) (Figure 2) with two beneficial isotopes, ^{10}B and Gd, for NCT was also synthesized and evaluated.

Method: In cellular uptake experiments using a human glioma cell line, U87MG, with high $\alpha_v\beta_3$ integrin expression, [^{67}Ga]**2** was added. After incubation for 1, 3, and 6 h, the radioactivity and the protein amount in cells was determined. In the biodistribution study, after approximately 10 days post-inoculation of U87MG into BALB/c nude mice, [^{67}Ga]**2** (37 kBq) was intravenously coadministered into tumor-bearing mice. Tumor-bearing mice were sacrificed at 1 and 4 h postinjection. Tissues of interest were removed and weighed, and their radioactivity was measured. U87MG cells treated with [^{10}B]**2** or [^{10}B]**3** were irradiated with neutrons, and the cytotoxicity was assessed by colony formation assays and WST assays.

Results: [^{67}Ga]**2** was synthesized with a radiochemical purity of over 95%. In cellular uptake experiments, the accumulation of [67Ga]**2** radioactivity in cells increased time-dependently. Furthermore, the biodistribution experiments in U87MG tumor-bearing mice, [^{67}Ga]**2** exhibited high accumulation in tumor at 1 h (7.09 ± 0.59%ID/g) and 4 h (6.65 ± 0.71%ID/g), respectively, and relatively low accumulation in other non-target tissues. In neutron irradiation experiments, both [^{10}B]**2** and [^{10}B]**3** demonstrated higher cytotoxicity than the control group without added drugs.

Conclusion: Compounds **2** and **3** show potential as theranostic probes. They can achieve tumor-selective delivery for NCT and prediagnosis by nuclear medicine imaging with the concept of using the same structural compound.

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Keywords: Nuclear Medicine, Theranostics

S1P16

BPA uptake and biological response to neutron irradiation of paediatric tumor cells

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Brain tumors in children are difficult to treat with standard radiotherapy due to potential severe adverse effects such as mental retardation, hormonal insufficiency or brain atrophy. Children are more vulnerable to such effects than adults [1]. BNCT, because it is a selective radiotherapy, can be a hope for these cases, as normal brain receives fewer doses than in standard radiotherapy. The only published clinical trials of BNCT for children with brain tumors are those from Nakagawa et al. [2], which date from the years when intraoperative BNCT was applied with the use of BSH as the boron compound. In spite of the fact that the results were promising, modern BNCT, based on epithermal neutron beams and the use of BPA has never been applied for paediatric cancers. Our aim is to provide preclinical data that may stimulate future clinical trials for children with brain tumors. In this study, we have measured the uptake of BPA by two different paediatric cell lines: SF8628, which corresponds to Diffuse Intrinsic Pointine Glioma, and Daoy, a medulloblastoma cell line. Diffuse Intrinsic Pontine Gliomas (DIPG) are highly aggressive and difficult to treat tumors arising in the ventral pons of the brain stem. Despite therapeutic advances, DIPG is incurable and most patients, primarily children, die within 2 years of diagnosis.
The analysis of the boron uptake has been performed by ICP-AES (Centro de Instrumentación Científica, University of Granada). In addition to this, the biological response to thermal neutron beam in BPA-treated cells has been studied by irradiation at the pure neutron line PF1b of the Institute Laue-Langevin (Grenoble), with a set-up developed by our group [2]. The biological response is observed by means of proliferation and clonogenic assays and compared with that of tumor cell lines of adults, for which BNCT has been successfully applied, like head and neck cancer or Glioblastoma Multiforme.
The results show a positive boron uptake and a biological response similar to adult cell lines, which encourages further research towards clinical trials of BNCT for paediatric brain tumors.

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Keywords: BNCT, paediatric tumor cells, DIPG

S1P17

CHEMICAL CANCERIZATION AND BNCT EFFECTS ON SALIVA PRODUCTION IN AN EXPERIMENTAL IN VIVO ORAL CANCER MODEL

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Head and neck cancer has a high incidence and mortality rate in cancer patients, oral cancer being one of the most frequent type of lesion. BNCT has been extensively studied as a potential strategy to treat these tumors. Although BNCT has significantly increased patient quality of life and survival, common adverse effects like mucositis (inflammation, ulcers and necrosis in the mucosa) and xerostomia (dry mouth) have been reported. Both radiotoxic effects could alter treatment and affect patient quality of life negatively. The experimental model of oral cancer in the hamster cheek pouch is scientifically validated to study tumor development, antitumor treatments and their associated toxicity. This model induces tumors surrounded by a precancerous tissue, the dose-limiting tissue in our BNCT studies. Our group evaluated, in this model, the therapeutic effect of BNCT mediated by different borated compounds and combined with strategies to increase antitumor effect. We also studied BNCT induced mucositis, but did not evaluate xerostomia after BNCT. The aim of this work was to evaluate if the chemical cancerization employed to induce the development of the tumors in the hamster cheek pouches and BNCT alter saliva production. We characterized saliva production in normal and cancerized animals, taking into account age and sex of the animals, and after BNCT mediated by boric acid + GB-10 (50 mg B/kg bw). Saliva production was measured during 10 minutes with absorbent endodontic cones placed inside the hamster´s mouth, under their tongue. The difference in the cone weight –CW- (CW 10 min – CW 0 min) was the saliva produced in 10 min (in mg). Saliva production was evaluated in different groups: [A] normal animals, both sexes, aged between 6-8 and 18-20 weeks; [B] cancerized animals, both sexes, evaluated immediately after finishing the cancerization process vs one month later (T30); [C] tumor-bearing animals treated with BNCT mediated by boric acid+ GB-10 (50 mgB/kg bw) evaluated at 7, 10, 14, 21 and 28 days after BNCT. Hamsters were cancerized with dimethylbenzanthracene twice a week for 12 weeks. BNCT in vivo studies were performed 3 h after i.v. injection of a solution of boric acid + GB-10 (BA, 25 mg ^{10}B/kg, iv + GB-10, 25 mg ^{10}B/kg). The animals were irradiated at the RA-3 nuclear reactor (Buenos Aires) at 5 Gy total absorbed dose to precancerous tissue (the dose-limiting tissue). Preliminary results showed that saliva production was independent of sex and age. We observed that the cancerization protocol employed did not affect hamster saliva production (20 normal pre-cancerization animals vs 19 cancerized animals, 5±2 mg vs. 5±2 mg). However, one month after the end of the cancerization protocol, where 18 of 19 animals had tumors (with volumes less than 100 mm^3), saliva production was increased (7±2 mg). Finally, 7 days after BNCT we observed a significant reduction in saliva production that was restored at 10 days after BNCT to pre BNCT values. This effect was maintained during the rest of the follow up. To conclude, in this work we observed that saliva production could be increasing due to tumor development. BNCT induced a transient reduction in saliva production 7 days after BNCT, matching with the peak of mucositis reported after BNCT in precancerous tissue. Future studies will be aimed at testing compounds that could avoid this reduction in saliva and study if this could be an effective treatment to avoid BNCT induced mucositis in the precancerous dose limiting tissue.

Keywords: oral cancer, hamster, xerostomia, BNCT

S1P18

First reported immunohistochemical studies and q-PCR expression of LAT-1 transporter in the hamster cheek pouch oral cancer model

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BNCT mediated by BPA (boronphenylalanine) has been studied in many clinical trials for different tumors with significant improvement in patient quality of life and survival. Our group has extensively studied BPA biodistribution, microdistribution and BNCT therapeutic effect in the hamster cheek pouch oral cancer model. This model closely mimics the events involved in the development of precancer and malignant human oral lesions. It provides a tumor model surrounded by precancerous tissue that gives rise to the formation of additional tumors and allows for the study of mucositis as occurs in field-cancerized oral mucosa in head and neck cancer patients. Mucositis is an inflammatory and ulcerative response in irradiated mucosa, limiting the treatment and patient quality of life. We previously demonstrated, in the hamster oral cancer model employing BPA, therapeutic boron concentration values in the tumor and preferential uptake by the tumor versus the surrounding precancerous and normal tissue. Additionally, we observed that BPA accumulates preferentially in tumor parenchyma rather than in stroma. BPA/BNCT in this in vivo model showed high tumor responses, however, severe mucositis in the precancerous surrounding tissue was reported. It is known that L-type amino acid transporter 1 (LAT-1) is mainly responsible for BPA uptake and it is significantly expressed in highly proliferative tissues and many cancer types. To explain the results mentioned above, the aim of this study was to evaluate, for the first time in the hamster cheek pouch oral cancer model, the expression of LAT-1 in tumors, precancerous and normal tissue through immunohistochemical and q-PCR studies. Syrian hamsters 6-8 weeks old were subjected to dimethylbenzanthracene (DMBA) cancerization twice a week for 12 weeks. Tumor-bearing hamsters were divided in two groups: No BPA injection (3 animals) versus BPA injected animals (3 animals, 15.5 mg ^{10}B/kg – approx. 300 mg/kg BPA). Based on our previous studies, 3 hours after i.v. injection of BPA, the animals were euthanized. The pouch bearing the tumors and the contralateral normal pouch were embedded in paraffin, then sectioned and stained for LAT-1 expression by immunohistochemistry using a rabbit anti-LAT-1 antibody (TransGenic Inc) followed by visualization using anti-rabbit HRP polymer and DAB. Additionally, a sample of tumor, precancerous tissue and normal pouch were digested to analyze LAT-1 gene expression by q-PCR using specific primers for LAT-1, and Rpl13a as the housekeeping gene to standardize the results. Immunohistochemistry showed that non-keratinized tumor cells are strongly positive for LAT-1. In the basal area of precancerous and normal tissue LAT-1 expression was positive, and apparently similar in both BPA injected and non-injected animals, across all samples. This would indicate that BPA accumulates in the epithelial basal layer and, after neutron irradiation, a cytotoxic reaction in these cells would trigger mucositis in precancerous tissue. Ongoing studies will determine if there are differences in the expression of LAT-1 between BPA injected and non-injected animals. Preliminary q-PCR results would suggest no differences between these groups.

Keywords: BNCT, LAT1, Immunohistochemistry, qPCR, BPA

S1P19

EVALUATION OF A BIMODAL COMPOUND DERIVED FROM LAPATINIB FOR THE TREATMENT OF UNDIFFERENTIATED THYROID CANCER (UTC).

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Undifferentiated thyroid cancer (UTC) is the most aggressive of thyroid cancers. It is a very rare tumor that is found in less than 2% of patients with thyroid cancer. This carcinoma is refractory to radioactive iodine (^{131}I) therapy and is typically treated with a multidisciplinary approach that includes surgery, radiotherapy and chemotherapy, showing a survival rate of 18% at one year (1). Previously in our laboratory we have demonstrated in preclinical studies that BNCT is feasible to be used for the treatment of UTC (2-4). The bimodal compounds derived from lapatinib are inhibitors of cellular tyrosine kinases that, when enriched with boron, are attractive for combining therapy directed at molecular targets and BNCT (5). Tyrosine kinases are molecules that promote cell proliferation, angiogenesis and metastasis, and are deregulated in tumor cells. The objective of this studie was to evaluate both the antitumor effect and the uptake of a drug derived from lapatinib enriched with boron (C14) in an experimental model of UTC.
Procedure: NIH nude mice 6 to 8 weeks' old were implanted in the right posterior flank with 10^6 cells of the human UTC cell line (8505C). After 20 days, the animals with tumors (25-50mm^3) were divided into 4 groups: 1) Control (n=5); 2) C14 (n=5); 3) BPA (n=5) and 4) C14 plus BPA (n=5). C14 was administered intraperitoneally every other day for 15 days at a dose of 0.01 µg/g b.w. The weight of the animals and tumor size were monitored during the treatment time. On the day of biodistribution, groups 3 and 4 were also administered with borophenylalanine (BPA) 350 mg/Kg b.w. One hour after injection, the mice were sacrificed and samples of tumor, blood and different tissues were taken. The samples were weighed and digested and the boron content was measured by inductive argon plasma atomic emission spectroscopy (ICP OES).
Results: The weight of the mice remained constant and without differences between groups during treatment ($p>0.05$) showing that C14 is nontoxic. The animals in groups 2 and 4 showed a decrease in relative tumor volume compared to the animals in groups 1 and 3, indicating an antitumor effect of the borated compound (C14) ($p<0.01$). The measurement of boron in the tumor showed a value of 4, 15 and 18 ppm for groups 2, 3 and 4 respectively. In groups 2, 3 and 4 the ratio of boron concentration between tumor and blood was greater than 3, demonstrating the selectivity of both compounds. Conclusions: The bimodal drug candidate (C14) could be used for the treatment of thyroid cancer by combined molecular target therapy to BNCT.

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Keywords: undifferentiated thyroid carcinoma, lapatinib, bimodal,

S1P20

Functionalized boron nitride nanoparticles as boron carriers in boron neutron capture therapy

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A key step in boron-neutron capture therapy is the selective delivery of boron to tumor cells and then irradiation of the affected area with a neutron beam. An important aspect in the development of BNCT is the search for compounds which allow the delivery of an effective concentration of boron to the tumor environment. An interesting aspect is the use of inorganic nanoparticles such as boron nitride. Due to the high content of boron and the possibility of surface modification of these nanoparticles, they may prove to be an extremely attractive tool in targeted BNCT (1).
We developed boron-rich nanoparticles that can be dedicated to boron neutron capture therapy as a potential carrier for the boron delivery to cancerous tissues. Functionalized carbonated boron nitride nanostructures were successfully synthesized in self-propagating combustion waves in the mixtures of high-nitrogen explosive and boron compounds. High thermal neutron capture cross-section of boron-10 enriched BN can be suitable for absorption and interaction of neutrons required in BNCT (2). The ZetasizerNano ZS instrument from Malvern was used to measure the diffusion coefficient by the dynamic light scattering, and the electrophoretic mobility by Laser Doppler Velocimetry technique. The hydrodynamic diameters were calculated using the Stokes-Einstein relationship and the zeta potential were calculated using the Smoluchowski model.
The cytotoxicity of the obtained boron nitride nanoparticles was assessed in the MTT assay on selected cell lines: MC38 cells of murine colon carcinoma, HT-29 cells of human colon adenocarcinoma cell line, RAW264.7 cells of mouse macrophage cell line, THP-1 cells of the human monocytic cell line. Using the flow cytometry technique, the interactions of FITC-labeled boron nitride nanoparticles with selected cells were examined and cell granularity analysis was performed. Additionally, in order to confirm the interactions of boron nitride with cells, fluorescence microscopy imaging was performed on the example of the RAW264.7 cell line.
The results of boron nitride synthesis in the combustion wave propagating in mixtures of TAGAZ with $NaBH_4$ or BH_3NH_3 demonstrated that it might be used to produce significant amounts of nanosized boron nitride powders with specific particle structure and chemical composition. Moreover, different efficiencies of binding and uptake of these nanoparticles by various cells – such as normal phagocytic cells or cancer cells resulted in significantly different cell viability and were related to their histological type. The initial observation suggests promising application of synthesized boron nitride in BNCT.

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Keywords: boron nitride, BNCT, cell lines

S1P21

In-Air Radiobiological Characterization of Neutron Beams of In-Hospital Neutron Irradiator-1 for Boron Neutron Capture Therapy

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Boron Neutron Capture Therapy (BNCT) entails a mixed radiation field with diverse components featuring different Linear Energy Transfers (LETs) and efficacies in tissue. The biological effects of BNCT arise from at least four distinct physical components contributing to energy deposition in both tumors and healthy tissue. The primary contributor to the biological effect in tumor tissue is the boron dose, representing the absorbed dose from α particles and ^{7}Li particles generated through the boron neutron capture reaction. Other contributing dose components include proton recoils resulting from fast-neutron interactions (^{1}H(n, n')p), 0.54 MeV protons from the nitrogen capture reaction (^{14}N(n, p)^{14}C), γ-rays contaminating the primary beam, and 2.2 MeV prompt γ-rays from hydrogen capture. Notably, the composition of these dose components varies based on the neutron energy spectrum of each utilized beam. For instance, the patterns of dose components in each beam differ across institutions.
To accurately evaluate the biological response of both tumor and healthy tissue to BNCT and to compare clinical results across institutions, it is imperative to determine all dose components and their Relative Biological Effectiveness (RBE) individually for each beam. This meticulous approach ensures precision in assessing the efficacy of BNCT and facilitates meaningful comparisons of clinical outcomes across diverse institutional practices. In this research, we conducted absorbed dose measurements and in vitro cell survival assays utilizing thermal and epithermal beams of IHNI-1. The aim was to RBE of each dose component for these beams, which had not been previously characterized at IHNI-1.
To determine the neutron flux, we employed the activation method using gold foils, both with and without cadmium covers. The neutron energy spectrum was subsequently computed using Monte Carlo Code simulations. V79 cells were loaded into cryotubes and exposed to varying durations of neutron irradiation after the addition of the appropriate concentration of boron agents boronophenylalanine (BPA). A control group, not exposed to neutron irradiation, was maintained. Post-irradiation, the cells underwent centrifugation, resuspension, and plating in 6-well plates with subsequent incubation in a CO_2 incubator, featuring regular media changes every 2 to 3 days. On the 7th day, cells were fixed with methanol, stained with crystal violet, and the quantification of cell colonies ensued. Plating efficiency was calculated based on the control group devoid of irradiation. Leveraging colony counts, seeded cell numbers, and plating efficiency, the survival fraction of cells under varied conditions was determined. A parallel survival curve for cells under X-ray irradiation was established through a colony formation assay. The absorbed dose ratio, computed as the ratio of a reference X-ray radiation dose to neutron radiation or Boron Neutron Capture Therapy (BNCT) dose, was determined at survival fraction values of 0.1 or 0.37. These values represent the relative RBE values of the neutron beams and also the boron agent.

Keywords: BNCT, Radiobiology, RBE, Neutron beam

S1P22

Non-targeted effects of BNCT: bystander and abscopal effects. An in vitro study.

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Until about 10 years ago, it was generally accepted that the effects of radiotherapy were mediated by the local effects of ionising radiation, which causes direct damage to DNA or indirect damage through free radicals generated by the radiolysis of water. However, this assumption has been challenged by numerous observations indicating that nearby or distant non-irradiated cells can sometimes exhibit the same response as irradiated cells.[1] This assumption originates from studies revealing that radiation generates "danger" signals, which can spread from irradiated to non-irradiated cells, causing "non-targeted effects". We can distinguish mainly two types of non-targeted effects. The radiation-induced **bystander effect** is a radiobiological effect that is transmitted from irradiated cells to neighbouring unirradiated cells, leading to biological changes in the recipient cells.[2] The radiation-induced **abscopal effect** is a local radiation-induced systemic effect that extends outside the treated volume, and is able to drive the regression and rejection of non-irradiated, distant tumor lesions.[3]
In recent years, bystander and abscopal effects have been studied in the context of Ray X and gamma radiotherapy or other innovative particle therapies such as proton therapy and carbon ion therapy. However, very little is known about possible non-targeted effects in the context of BNCT.
To address this question, we investigated the potential bystander and abscopal effects of **Cal33** (head and neck cancer) and **A172** (glioblastoma) cell lines irradiated under BNCT-equivalent conditions, via in vitro methods. To this end, these cell lines, previously treated with Boron Phenylalanine (**BPA**) were irradiated with a thermal neutron beam at the nuclear reactor of the **Institut Laue-Langevin** (ILL) in Grenoble (France). Cells were then incubated, and the supernatants (**conditioned media**) were collected 24 and 48 hours after irradiation. Subsequently, we incubated different cells, namely non-irradiated Cal33 and A172 cells (for bystander effect) and peripheral blood lymphocytes (for abscopal effect), with the previously collected conditioned media.
To study the bystander effect, we performed invasion assays, while migration and phenotypic assays were carried out to study the abscopal effect. In addition, the presence of various cytokines and chemokines associated with these effects[4], were studied in the conditioned media. To compare the non-targeted effects of BNCT with those of gamma-ray radiotherapy, cells were irradiated with photons at a linear medical accelerator (Hospital Universitario Virgen de las Nieves, Granada, Spain). The conditioned media were collected and used as previously indicated.
Preliminary findings suggest that **there are differences** between the abscopal and bystander effects produced by irradiation of A172 and Cal33, both under gamma irradiation and BNCT conditions. These results correlate with those obtained in assays previously performed by the group to analyse the sensitivity of these cell lines to both types of radiotherapy (gamma and BNCT). Overall, these data demonstrate the **relevance of non-targeted effects** and encourages further research in different types of tumor cells, particularly in the **BNCT scenario.**

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Keywords: BNCT, abscopal, bystander, Cal33, A172.

S1P23

Role of transmembrane channel-like 5 (TMC5) in boron neutron capture therapy

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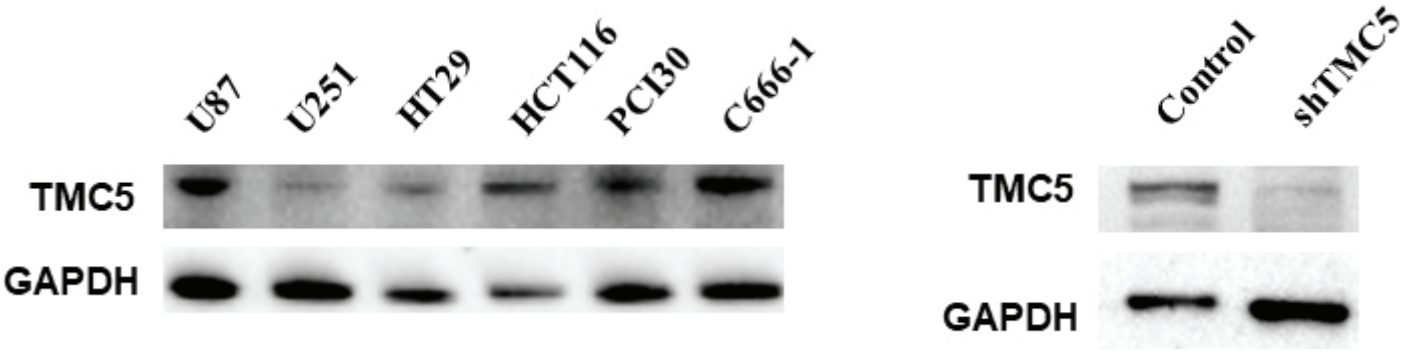

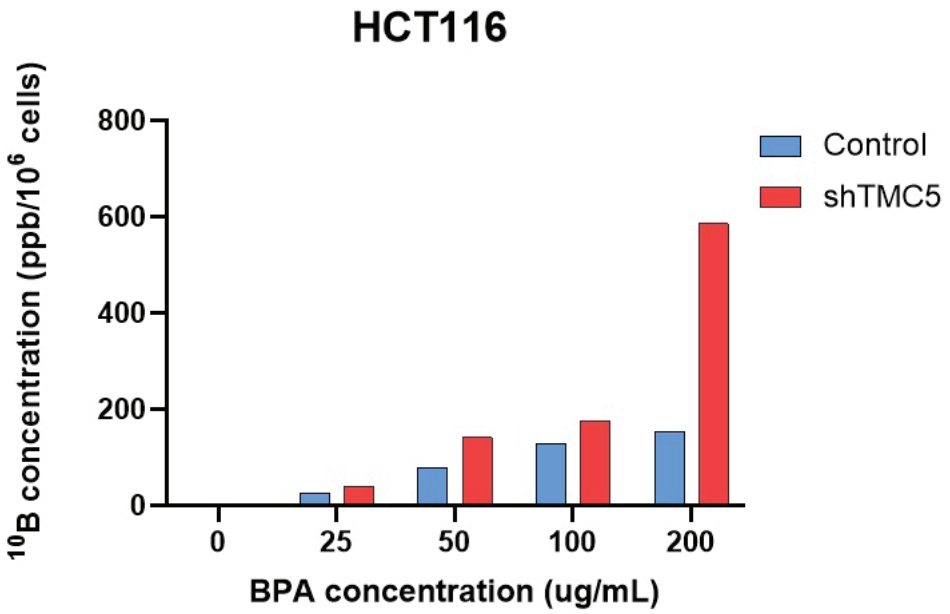

Figure captions:
Figure 1 TMC5 expression in different cancer cell lines;
Figure 2 Knockdown of TMC5 by lentiviral transduction in HCT116 cells;
Figure 3 10B concentration in shTMC5 group compared with control group

Boron neutron capture therapy (BNCT) has proven to be an effective treatment for a range of cancers. The selective uptake and accumulation of boron in tumor cells will improve BNCT to be a more promising radiotherapy for high precision cancer treatment. It is recognized there are opportunities to improve upon ^{10}B uptake concentration and micro-distribution by exploring the role of selected targets on the influence of ^{10}B delivery, and the downstream therapeutic effect, towards identifying potential targets and biomarkers for BNCT. Transmembrane channel-like 5 (TMC5) belong to a larger trans membrane channel-like (TMC) gene family. TMC proteins are modifiers of ion channels or transporters, directly or indirectly participating in regulating the permeability of cell membrane channels. The expression level of TMC5 is significantly higher in tumor tissue than that of the normal tissue in most cancer types according to a bioinformatic study(1). Towards understanding the role of

TMC5 on boronophenylanine (BPA) accumulation in tumor cells, the expression levels of TMC5 in different human cancer cell lines (glioma: U87 and u251, colorectal cancer: HT29 and HCT116, head and neck cancer: PCI30 and C666-1) have been analyzed by Western blot (Figure 1). Then, we transduced short hairpin RNA (shRNA) to knockdown TMC5 in HCT116 colorectal cancer cell line, selected due to demonstration of a relatively high expression of TMC5 (Figure 2). The knockdown and corresponding control cells were treated with clinical-grade ^{10}B-BPA with a concentration of 25, 50,100, 200μg/mL, and the intracellular ^{10}B concentration across different groups quantitatively measured by using inductively coupled mass spectrometry (ICP-MS), with the capability to detect ^{10}B concentrations as low as 0.1 ppb. A preliminary study found that the ^{10}B concentration in the TMC5 knockdown group was higher than the control group for all tested BPA concentrations (Figure 3). Our future work will clarify the role of TMC5 on boron transportation and BNCT efficacy in a range of relevant cancer types such as head and neck cancer and glioma. It is hoped that through the efforts of further study, the role and mechanism of TMC5 on BNCT will be unveiled, and novel strategies targeting TMC5 will expand BNCT indications, and unlock the potential of BNCT being highly effective and less toxic, benefiting cancer patients.

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Keywords: BNCT; Boron delivery; TMC5

S1P24

SEQUENTIAL BORON NEUTRON CAPTURE THERAPY (BNCT) IN A MODEL OF DIFFUSE LUNG METASTASES IN BDIX RATS.

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It is known that the lung is one of the most common site of metastasis, due to its rich vascularization and lymphatic drainage characteristics. One of the most frequent primary tumors that disseminate to the lung is colorectal cancer. Treatment options include surgery, radiotherapy and chemotherapy, however, survival has not been improved. In this context, there is a need of more precise, selective and less toxic treatment strategies. BNCT would be an interesting option for this pathology. BPA (borophenylalanine) has been extensively studied in BNCT clinical trials for the treatment of different pathologies. It is incorporated by tumor cells through LAT transporters (L-type amino acids), which are overexpressed in metabolically active cells. BPA preferentially locates in the tumor parenchyma, favoring tumor control. However, BPA is also incorporated into the basal layer of the skin inducing dermatitis, an unwanted adverse effect. On the other hand, GB-10 (decahydrodecaborate) is a diffusive compound that preferentially accumulates in tumor stroma, which was once approved by the FDA for its use in patients. The combination of two boron compounds with different uptake and microdistribution mechanisms would increase BNCT tumor control while reducing their associated side effects. In previous studies by our group in the hamster cheek pouch oral cancer model, we demonstrated the therapeutic advantages of Sequential BNCT employing these two boron compounds, i.e. BPA-BNCT and, 24h later, GB-10-BNCT. Besides, in an ectopic colon cancer model, we also demonstrated the BNCT abscopal effect on those tumors that were not located in the irradiation field. Based on these reports, the aim of the present study is to evaluate tumor control, radiotoxicity and the abscopal effect of a Sequential BNCT protocol with a 7 days interval between irradiations (BNCT-Seq-7days) in an experimental model of diffuse lung metastases employing BPA and GB-10. Syngeneic DHD/K12/TRb colon cancer cells were injected intravenously (iv) into BDIX rats. 3 weeks later, BPA-BNCT (T0) was performed at the RA-3 nuclear reactor (Buenos Aires) employing BPA (46.5 mg ^{10}B/kg, intraperitoneal injection –ip-). 7 days after BPA-BNCT, the same group of animals was treated with (GB-10)-BNCT (50 mg ^{10}B/kg, ip). To evaluate the abscopal effect, 24h after (GB-10)-BNCT, DHD/K12/TRb cells were inoculated subcutaneously in the right hind flank of the animals treated with BNCT-Seq-7days. To assess lung metastases response to BNCT, the clinical signs of the animals were monitored for 5 weeks from T0, evaluating body weight and measuring oxygen saturation and respiratory rate (with a pulse oximeter). Additionally, we evaluated dermatitis in the exposed skin area. The abscopal effect was assessed measuring the volume of the ectopic tumors developed on the right hind flank. After euthanasia, we evaluated the lung mass and metastases spread in the lung (histologically and employing a Bouin's solution to visualize macroscopically the nodules). Finally, cytometry analysis was performed to study the immune cell population present in the rat leg lymph node that corresponds to the ectopic tumor, the ectopic tumor microenvironment and those immune cells present in the lung with metastases. All these parameters were also evaluated in Sham animals (same manipulation without treatment, control group) and normal animals when necessary. Ongoing preliminary studies will allow us to set the best irradiation conditions, based on the therapeutic and radiotoxic effects studied in this experimental model of diffuse lung metastases in BDIX rats. The fact that these two boron compounds were used in patients will bridge the gap between experimental and clinical studies, being a time and cost effective strategy to improve BNCT.

Keywords: BNCT, Lung metastases, BPA, GB-10,

S1P25

Boron Neutron Capture Therapy (BNCT) mediated by boric acid + GB-10: biodistribution and BNCT studies in an experimental oral cancer model

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BNCT therapeutic efficacy depends on the biodistribution and microdistribution of the boron agent in the tumor and the dose limiting tissues in the target volume. New boron compounds are currently under development. However, many years of studies and very high costs will be necessary for these new compounds to be approved for their use in humans. In this sense, optimizing the delivery of boron compounds that were/are already approved for clinical studies would allow a more direct and less costly process. Boric acid and decahydrodecaborate (GB-10) are low molecular weight boron compounds like BPA and BSH. They have diffusive characteristics. Boric acid was one of the first compounds used in BNCT clinical trials in the 1950s–1960s. GB-10 was once approved by the US Food and Drug Administration for its use in patients. Head and neck cancer is one of the most well studied targets for BNCT, oral cancer being the most frequent type. Our group studies BNCT in the hamster cheek pouch oral cancer model, which allows for the study of tumors surrounded by a precancerous dose-limiting tissue. In this model, we previously performed biodistribution and BNCT studies employing GB-10 or Boric Acid (BA), both at 50 mg^{10}B/kg. Although BA exhibited significantly higher boron accumulation in the tumor than GB-10, BA/BNCT induced higher radiotoxicity (in terms of mucositis) than GB-10/BNCT in the precancerous tissue surrounding tumors. Based on these results, the aim of the present study is to combine BA+GB-10 at a total dose of 50 mg^{10}B/kg, to increase BNCT therapeutic effect while reducing radiotoxicity in precancerous tissue. Boron biodistribution studies employing two administration protocols of BA+GB-10 (50 mg^{10}B/kg) were performed in tumor bearing animals: (Protocol 1) BA+GB-10 (35+15) mg ^{10}B/kg, i.v.; (Protocol 2) BA+GB-10(25+25) mg ^{10}B/kg, i.v. Three hours after the administration of BA+GB-10, blood, tumor, precancerous tissue and normal pouch tissue samples were processed for absolute boron concentration measurements by ICP-OES. Based on biodistribution results, BNCT in vivo was performed employing Protocol 2, i.e. BA+GB-10 (25+25) mg ^{10}B/kg. Tumor response and radiotoxicity were evaluated during 28 days after BNCT and compared with our previous BNCT studies mediated by BA (50 mg^{10}B/kg). The animals were irradiated at the RA-3 nuclear reactor (Buenos Aires). The total absorbed dose to precancerous tissue (the dose-limiting tissue) was 5.0 to 5.2 Gy. Regarding the biodistribution results, mean boron concentration (ppm) in the tumor was significantly higher for Protocol 1 vs Protocol 2 (44.2 ± 12.8 vs 29.3 ± 13.2, respectively, p=0.0401). For both protocols, these values are therapeutically useful in BNCT (higher than 20 ppm). However, boron concentration in precancerous tissue and normal pouch tissue was higher for Protocol 1 vs Protocol 2 (43.4 vs 28.5 and 41.7 vs 28.6, respectively), potentially leading to higher induced radiotoxicity when employing BNCT mediated by Protocol 1. Based on these results, we treated the animals with BNCT mediated by Protocol 2. We observed a significantly higher percentage of tumors with overall (OR) and complete responses (CR) for both BNCT groups vs the sham (cancerized not treated) and beam only groups (p<0.0001). BA/BNCT and BA+GB-10 (P2)/BNCT exhibited a high and similar percentage of OR and CR responses (86% vs 69% and 48% vs 47%, respectively). However, we observed that BA+GB-10 (P2)/BNCT exhibited a significantly lower percentage of animals with severe mucositis vs BA/BNCT (0% vs 72%, p<0.0210). In this study we demonstrated that BNCT mediated by Protocol 2 was therapeutically effective to treat tumors and induced only slight to moderate mucositis. Future studies will be aimed at increasing the dose to precancerous tissue, expecting to increase BNCT therapeutic effect on tumors.

Keywords: Biodistribution, Boric acid, GB-10

S1P26

Verification of the efficacy of a novel boron drug using a phenylboronic acid-containing supramolecule.

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Boron neutron capture therapy (BNCT), which irradiates neutrons to boron (^{10}B) accumulated in cancer cells, has recently been started as a fifth modality for cancer treatment. BNCT, which relies on the nuclear reaction between accumulated boron and thermal neutrons, exhibits a distinctive feature of selectively destroying only cancer cells. While the currently clinically used boron compound, borophenylalanine (BPA), has shown therapeutic effects, it poses challenges such as rapid cellular excretion. Conversely, the novel boron compound, 4-Carboxy-3-fluorophenylboronic acid-Polyrotaxane (FPBA-PRX), operates differently from BPA, suggesting a potential resolution to the issues associated with BPA. This study aimed to evaluate the efficacy of the novel boron compound FPBA-PRX and demonstrate its potential as a new drug for BNCT. The in vivo and in vitro experiments in this study utilized FPBA-PRX developed by Associate Professor at Kumamoto University. Targeting sialic acid, the study focused on Colon26 cells with high sialic acid expression. In the cytotoxic study using an MTT assay, a significant cell death was confirmed by continuously processing for more than 12 h with more than 12.5 mg/ml high concentration. In toxicity study in vivo, no significant weight loss was observed in the 2000 mg/kg FPBA-PRX group compared to the non-treated group, nor were there any changes in appearance abnormalities or blood cell counts. The boron concentration in blood and tumor after FPBA-PRX, FPBA and BPA-F (BPA fructose complex) administration were evaluated using ICP-AES. Colon-26 cells ($1x10^6$ cells/10 μL) were transplanted into the right lower limb of 9-10W BALB/c mice, and each drug was administered when the tumor grew to a diameter of 7-8 mm. FPBA-PRX and FPBA were treated with the drug for 18 hours, and BPA-f was treated with the drug for 2 hours. The 10B concentration has been unified to 35 ppm (1440 ppm condition has also been added for BPA-f). As a result, FPBA-PRX showed higher tumor and blood boron concentrations than FPBA without supramolecular structure, and only slightly lower than BPA-f. To investigate the anti-tumor effects, the same mouse model of colorectal cancer used in the drug kinetic study was used, and the tumor area was irradiated with neutron beams after administration of each drug. The tumor size of the mice was measured for 35 days after irradiation, a tumor growth curve was obtained, and the antitumor effect was confirmed. When the 10B concentration was the same at 35 ppm, FPBA-PRX showed a stronger antitumor effect than not only FPBA but also BPA-f. The above results suggest that FPBA-PRX is a new boron drug, including the possibility that a safe and effective BNCT can be implemented with a smaller boron concentration. In the future, research will be conducted focusing on re-evaluation of administration conditions, drugs, and intracellular drug distribution.

Keywords: BNCT,phenylboronic acid,sialic acid,supermolecule

S1P27

Study of the Boron-10 microdistribution in bone employing the neutron autoradiography technique

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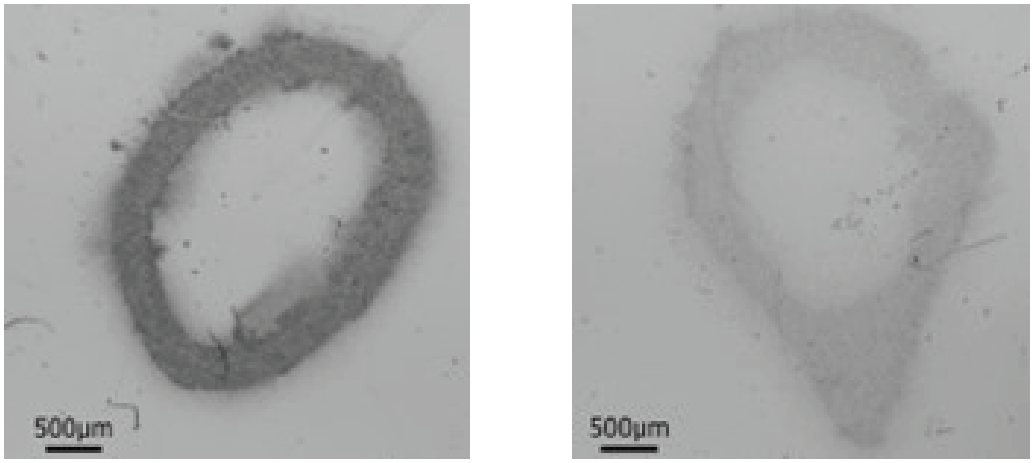

Figure captions: Figure 1. Examples of qualitative autoradiographs of femur sections (BA 200, a) and tibia (BPA 40, b). Original magnification: 2.5X.

Previous studies in our laboratory aimed to quantify boron in hard tissues, such as bone within a large animal model (e.g., sheep) infused with boronophenylalanine-fructose (BPA-F) using neutron techniques such as neutron autoradiography with nuclear track detectors (NTDs) [1]. The present study focused on optimizing the neutron autoradiography technique to address the microdistribution of different boron compounds in bone in a small animal model (Wistar rats). With this aim, new methods for obtaining bone samples without boron loss were developed. The samples were subsequently characterized and quantified, and the sample preparation process for irradiation was refined.
The rats were infused (intraperitoneal injection) with the following compounds: a) boric acid (BA), and b) BPA, at a dose of 40 ppm of boron (830 mg BPA/kg bw and 229 mg BA/kg bw, respectively), and c) boric acid at a dose of 200 ppm of boron (1144 mg BA/kg bw). The selected bone samples were the tibia and femur which were excised 3 hours post-infusion [2]. Thin bone sections were sliced using a diamond saw which were worn down to the desired height and polished with the use of multiple double sided diamond disks and wet sandpaper. Afterwards, an optical profilometry characterization (Veeco/Wyko® NT1100) was conducted to determine the optimal method for obtaining thin bone samples. The following step consisted of irradiating the samples. They were placed in close contact with polycarbonate sheets which were used as NTDs and irradiated with thermal neutrons at different fluences, 10^{12} n.cm^{-2} and 10^{13} n.cm^{-2} for quantitative and qualitative analysis, respectively. Thereafter, the polycarbonate sheets underwent a chemical etching process using a 70°C KOH solution to amplify the tracks on the NTDs, which were then observed using optical microscopy, as seen on Figure 1. For qualitative analysis, the sheets were etched for 2 min, whereas for qualitative analysis the time was set at 4 min.
The results from profilometry revealed that the wearing method using diamond disks produced thinner slices (~240 µm) with less roughness (~26.5 µm) compared to wet sandpaper, which yielded thicker slices (~582 µm) with higher roughness values (~44 µm). Finally, it was observed that the boron distribution is homogeneous throughout the tissue. This conclusion was reached after verification through qualitative analysis by studying the shades of gray in the autoradiographs. The correlation between the number of detected tracks and the shades of gray, as well as the homogeneity of the boron distribution, were confirmed through quantitative analysis, which involved traversing the bone samples and counting the observable events.

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Keywords: BPA, Boric-Acid, neutron-autoradiography,bone,boron-imaging

S1P28

Boron neutron capture therapy using direct intratumoral administration of a folate receptor targeting novel boron carrier

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Background: Boron Neutron Capture Therapy (BNCT) is a precise particle radiation therapy known for its unique cellular targeting ability, and has attracted attention as a treatment for malignant gliomas. The development of innovative boron carriers is crucial for BNCT advancement. Our preliminary research showed that BNCT with pteroyl-closo-dodecaborate-conjugated 4-(p-iodophenyl) butyric acid (PBC-IP), which contains ten B^{10} atoms (closo-dodecaborate), may be a promising treatment for malignant gliomas. PBC-IP features folate receptor α (FRα) targeting, enabling higher boron concentration within tumor tissues, such as malignant gliomas, where FRα is significantly overexpressed compared to normal tissues. Our previous study demonstrated the remarkable potential of PBC-IP administered via Convection-Enhanced Delivery (CED) in the F98 rat glioma orthotopic model. BNCT with PBC-IP CED administration significantly prolonged survival time compared to BNCT with boronophenylalanine (BPA) intravenous administration (i.v.) (p=0.003 in the log-rank test). In addition, half of the group of BNCT with PBC-IP CED administration showed long-term survival individuals (more than 90 days), which were not observed in the group of BNCT with BPA i.v.. This study is divided into two main parts. First, we examine how much the therapeutic effect decreases when the catheter is positioned at the periphery of the tumor core. Second, we explore the acceptable timeframe between the end of administration and the commencement of treatment.

Methods: In comprehensive in vivo experiments conducted on the F98 rat brain tumor orthotopic model, we meticulously examined boron distribution, neutron irradiation experiments at various CED administration sites, and multiple time intervals following CED administration. In the biodistribution experiment, the biodistribution from 1 h to 48 h after CED administration was examined, and the CED administration sites were prepared for three groups; 1. catheter insertion into the tumor center (original implantation site; 1mm posterior to bregma, 4mm to the right lateral side), 2. catheter placement at the tumor border (2 mm posterior to implantation site), and 3. contralateral brain catheter insertion (1 mm posterior to bregma, 4 mm to the left lateral side). The designs of the neutron irradiation experiment were as follows: A: 1) PBS CED administration , 2) PBC-IP CED administration , 3) neutron irradiation after termination of PBS CED administration , 4) neutron irradiation at 3 h after PBC-IP CED administration , 5) neutron irradiation at 6 h after PBC-IP CED administration , 6) neutron irradiation at 24 h after PBC-IP CED administration. B: 1) untreated group , 2) neutron irradiation at 3 h after PBC-IP CED administration in the contralateral brain of the tumor , 3) neutron irradiation at 3 h after PBC-IP CED administration in the peritumoral brain, and 4) neutron irradiation at 3 h after PBC-IP CED administration in the peritumoral brain in the tumor body.

Results: Notably, PBC-IP showcased substantial efficacy for BNCT, revealing minimal differences in tumor boron concentration between “tumor center” and “tumor border” CED administrations, though a gradual decline in intratumoral boron concentration post-administration was observed. The therapeutic efficacy remained robust, particularly when employing cannula insertion at the “tumor border” compared to “tumor center” injections. Even delayed neutron irradiation preserved notable effectiveness, albeit with a slightly reduced survival period. These findings underscore the robust clinical potential of CED-administered PBC-IP for the treatment of malignant gliomas, offering adaptability across an array of treatment protocols.
Conclusions: The novel boron carrier, “PBC-IP,” emerges as a highly promising agent for BNCT, demonstrating significant potential in the management of malignant gliomas. The application of BNCT with PBC-IP via CED administration unveils a promising avenue for treatment. Future investigations and preclinical trials are warranted to fully explore this exciting therapeutic avenue.

Keywords: Boron neutron capture therapy (BNCT),

S1P29

BIOINFORMATIC ANALYSIS OF POSSIBLE NEW BORON CARRIERS FOR THE APPLICATION OF BORON NEUTRON CAPTURE THERAPY (BNCT) TO THE ANAPLASTIC THYROID CANCER (ATC)

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Introduction: Boron neutron capture therapy (BNCT) is a binary treatment modality for malignant tumors based on the administration of boron compounds and subsequent irradiation of the tumor area with epithermal/thermal neutrons. In our laboratory we have previously shown that BNCT is a possible alternative for the treatment of anaplastic thyroid cancer (ATC). For BNCT to be effective, borated compounds must have ideally the following requirements: Selectively concentrate within tumor cells during irradiation time (minimum concentration of 10^9 of ^{10}B atoms per cell or 20-35 µg ^{10}B/g tissue), achieve a concentration ratio between tumor and normal tissue/blood equal to or greater than 3 and not be toxic when reaching the necessary tumor concentrations. A recent study has examined samples from patients with different types of thyroid cancer (ATC: anaplastic thyroid cancer, PTC: papillary thyroid cancer, and FTC: follicular thyroid cancer) and conducted a transcriptomic analysis of these samples using RNA-seq, making the databases available to the public.
Objective: Perform a bioinformatic analysis to identify solute transporters overexpressed in patients with tyroid carcinoma and thus design associated solutes that could be enriched with ^{10}B atoms and deliver boron at high concentrations.
Materials and Methods: Sequencing data deposited in Gene Expression Omnibus (GSE123868) from ATC (n=10) and healthy thyroid tissue (n=6) were analyzed using the Use Galaxy platform. Quality control was performed with FASTQC, genomic alignment with HISAT2 (hg38) and read counting with feature count. Differential expression analysis was carried out with the R edgeR package, considering a logFC>1 or logFC<-1 and FDR < 0.01 as significant expression. The gene ontology was checked with the R package pathfindR.
Results: The bioinformatic analysis identified 131 solute transporter genes with differential expression, of which 96 had higher expression in tumor tissue than in healthy tissue. Six genes with high tumor expression and their specific solutes were detected: LAT1 (logFC 7.09, neutral amino acids), MCT4 (logFC 4.41, monocarboxylates), OAT1 (logFC 3.71, p-aminohipurate), RFVT2 (logFC 3.67, riboflavin), SMIT2 (logFC 3.10, myo-inositol) and SMIT2 (logFC 3.06, pyrimidines).
Conclusions: The identified transporters in this work offer new opportunities for the development of new boron compounds for clinical use such as p-aminohipurate, riboflavin and myoinositol.

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"Studies for the application of boron neutron capture therapy to the treatment of differentiated thyroid cancer". Dagrosa A, et al.Applied Radiation and Isotopes 69(12):1752-5; 2011. Keywords: BIOINFORMATIC, BORON CARRIERS, ANAPLASTIC THYROID

S1P30

cRGD:MID:BSA FOR THE TREATMENT OF HEAD AND NECK TUMORS: PRELIMINARY BIODISTRIBUTION AND MICRODISTRIBUTION STUDIES IN THE HAMSTER CHEEK POUCH ORAL CANCER MODEL

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The development of new boron compounds is of utmost interest in the field of Boron Neutron Capture Therapy. In this sense, nano carrier-based boron delivery systems have been developed to improve the efficacy of BNCT, where serum albumin is used as the drug delivery mechanism. Previously, maleimide-functionalized closo-dodecaborate albumin conjugate (MID:BSA) was proved effective as a boron-10 carrier for BNCT in a glioma-bearing rat brain tumor model, in an ectopic colon cancer model in mice and in the hamster cheek pouch oral cancer model. However, there is room for improvement in terms of its biological targeting to tumor cells. In a recent study it was demonstrated that BNCT mediated by cRGD:MID:albumin improved BNCT survival in a rat glioma model. cRGD (cyclic arginine-glycine aspartate) is a known selective inhibitor of integrin αvβ3. This new boron compound has antitumoral and biologically boron target characteristics, as integrin αvβ3 is overexpressed in many cancer cells and plays a key role during angiogenesis, tumor progression and metastasic spread. Several studies have described $\alpha_v\beta_3$ integrins as a selective target of neovasculature in head and neck squamous cell carcinomas. It is known that oral cancer is one of the most common head and neck cancers in the World. With this in mind, in this study, we evaluated cyclic RGD-functionalized closo-dodecaborate albumin conjugates with maleimide (cRGD:MID:BSA) in the hamster cheek pouch oral cancer model. This model allows us to study oral tumors, the dose-limiting precancerous tissue surrounding the tumors and various clinically relevant normal tissues. MID was conjugated to BSA and cRGD in phosphate-buffered saline (PBS) by stirring the solution during 12 h at 37°C. The final solution was yellowish and clear. Hamsters 6-8 weeks old were cancerized with dimethylbenzanthracene twice a week for 12 weeks. Tumor bearing animals (n=5) were used for biodistribution/microdistribution studies. cRGD:MID:BSA (15 mgB/kg b.w.) was injected intravenously at a very slow rate to avoid acute toxicity caused by BSA, i.e., 0.05–0.1 mL every 30/60 s. Tumor, precancerous and normal pouch tissue and blood were taken 19 h after cRGD:MID:BSA injection. Samples were digested, weighed and processed by acid digestion for 1 hour at 100°C for measurement by ICP-MS. Additional normal tissues were stored for future measurement. All conditions were based on our previous studies performed in this in vivo model employing MID:BSA alone. These preliminary biodistribution results have shown that, employing cRGD:MID:BSA, absolute tumor boron uptake was significantly improved ($p<0.0001$) vs our previous studies with MID:BSA, i.e. 140.5±30.1 ppm (n=10 tumors) vs 31.7±11.1 ppm (n=27 tumors). Ongoing autoradiographic studies are currently evaluating cRGD:MID:BSA microdistribution in the tumor. Tumor/blood and Tumor/precancerous tissue were higher vs MID:BSA alone at the same dose (1.3 vs 1.6 and 1.7 vs 1.3, respectively). However, absolute boron concentration in blood and precancerous tissue have significantly increased ($p<0.0001$) vs MID:BSA (104.5±46.2 vs 23.2±9.0 ppm, 81.1±20.6 vs 24.3±11.3, respectively). These results need careful evaluation due to potential BNCT associated radiotoxic effects. Future studies will be aimed at lowering boron concentration values in blood and precancerous tissue. Recent studies in a glioma in vivo model have shown that 24 h post cRGD:MID:BSA injection, boron concentration in blood was reduced but boron concentration in the tumor remained similar and high.

Keywords: oral cancer, hamster, cRGD:MID:BSA, biodistribution

Session 2

S2P1

Design of a compact accelerator-driven neutron source with 2 epithermal neutron ports for boron neutron capture therapy

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Accelerator-based boron neutron capture therapy (AB-BNCT) has been witnessing increased attention in recent years, thanks to the low cost, low irradiation level and compact size of compact accelerator-driven neutron source (CANS) compared to reactors. However, the Beam Shaping Assembly (BSA) of CANS needs to be carefully designed to effectively utilize the produced neutrons due to its low neutron yield. Usually, the CANS dedicated to BNCT have one beam port for the treatment or have multiple ion beamlines with a specific 1-port BSA. A reactor-based neutrons sources for BNCT can achieve more treatment beam ports easier than CANS because of its high neutron yield. In this work we demonstrate that a CANS can have 2 epithermal neutron ports in a BSA and fully satisfy the IAEA criteria published in 2001.
The simulation was done by the software Monte Carlo N-particle transport (MCNP 6), assuming the proton beam is 2.5 MeV 10 mA and the Li target is 100 um thick and 10 cm in diameter. The JENDL-4.0HE library is used for the step of neutron production and the ENDF/B-VIII is used in the following steps of neutron transport. The dual moderator consists of MgF_2 moderator at 45° with respect to the proton beam direction and AlF_3 moderator at 60° with respect to the proton beam direction. A Ti filter covers the top of MgF_2 moderator to absorb fast neutrons.
The MgF_2 port delivers softer neutron spectrum than the AlF_3 port, and the AlF_3 port gives higher epithermal neutron flux than the MgF_2 port. The modified Synder head was used for the in-phantom study. It is shown that the head phantom receives a higher dose rate from AlF_3 port than that from the MgF_2 port. However, there are only very small differences in the advanced depth, double dose depth and triple dose depth between the MgF_2 port and AlF_3 port. Therefore, a moderator of CANS made with symmetrical MgF_2 at two ports providing identical irradiation field may be a more practical design to prevent accidents happening at one beam port.

Keywords: BNCT, CANS, BSA, 2 ports

S2P2

Development of A Measurement Method for Neutron Spectrum in Epi-thermal Energy Range by Combining Activation Foils and Position-sensitive Proportional Counter -Numerical Study-

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We have developed a low-energy neutron spectrometer for BNCT since the energy spectrum is important for assessing patient response and planning the treatment [1]. Although several approaches have been examined to measure it, there are few approaches to evaluate it accurately [2-4]. A unique approach has been developed in my laboratory using a position-sensitive proportional counter [5]. It can obtain the signal corresponding to the position where neutrons react with the counting gas. We used ^{3}He as a counting gas, which has a high cross-section for low-energy neutrons, and the cross-section has a one-to-one correspondence with the neutron energy [6]. Therefore, lower-energy neutrons react in the shallow region and higher-energy neutrons react in the deeper region. The reaction depth distribution is converted into the energy spectrum using a suitable spectrum unfolding method [7]. Validation of this method is underway and we have found that this spectrometer applies to the neutron energy range of 0.5 eV to 1 keV. However, due to the low energy resolution in higher energy regions, it doesn't seem easy to measure the energy spectrum for over 1 keV [5]. In BNCT, the energy range of the neutrons is as high as 10 keV, so it is necessary to extend the possible measurement range. To solve this problem, we have utilized additional activation foils. The multiple foil activation method is applied to measure the energy spectrum. By adding activation foils, we could extend the measuring energy range. In this presentation, we report the result of the numerical study. The procedure of the numerical study is as follows; Firstly, several materials with high thresholds in the range of 10 keV to 10 keV were selected for the activation foils. JENDL-5.0 [6] is used as the cross-section library. Then the activities of the selected foils were calculated by numerical simulations. F4 Tally in MCNP 5 [8] was used to estimate the foil activities. Finally, the two sets of data, reaction depth distribution and foil activities, were combined and converted into the energy spectrum by the spectrum unfolding process using the Bayesian estimation method. The energy spectrum obtained was then compared with the one calculated by MCNP5. As a result, these two values of the energy spectrum were confirmed to be in good agreement with each other. We are currently preparing the validation experiment.

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Keywords: Neutron Spectrometer, Spectrum Unfolding

The epithermal neutron flux detectors developed for BNCT

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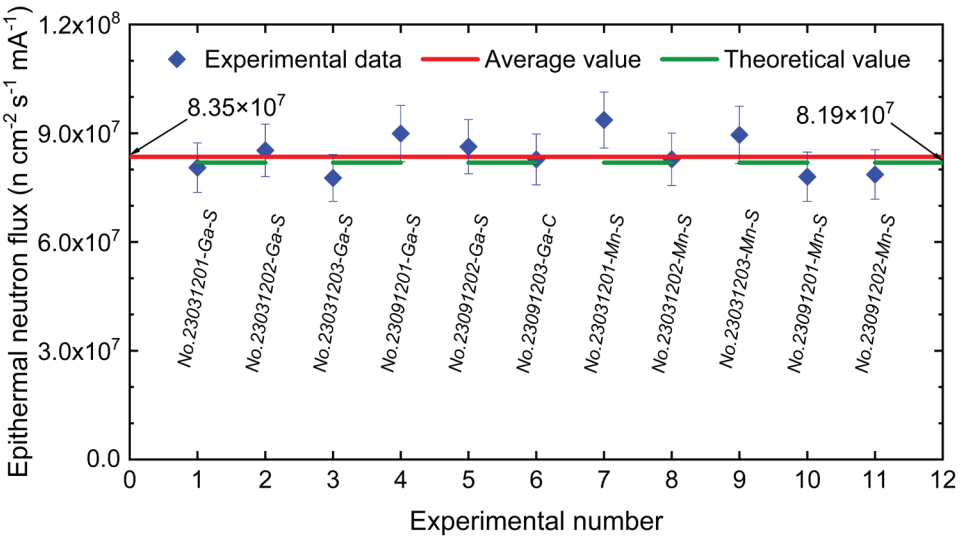

Figure captions: Graphic 1. Experimental results

Boron neutron capture therapy (BNCT) is a unique type of radiotherapy, which combines an external neutron beam with appropriate energy and high-intensity and a ^{10}B-containing compound that selectively accumulates in tumor cells. In recent years, BNCT has attracted a great deal of attention around the world as the next-generation radiotherapy especially for treating refractory and recurrent tumors. BNCT requires high-flux (≥ 5 × 10^8 n cm^2 s^{-1}) epithermal neutron (0.5 eV to 10 keV) beam to treat deep-seated tumors. Therefore, it is of great importance to evaluate the epithermal neutron flux in BNCT because it is directly related to the BNCT treatment beam quality assurance (QA) and radiation dose evaluation in treatments and clinical trials. We developed some novel detectors using ^{71}Ga(n,γ)^{72}Ga or ^{55}Mn(n,γ)^{56}Mn reaction to measure the epithermal neutron flux of BNCT treatment beam. Theoretical and experimental studies have demonstrated the good performance of these detectors. In this study, we experimentally evaluated the performances of these detectors at the accelerator-based BNCT (AB-BNCT) device developed by Lanzhou University, which is installed at the Fujian Medical University Union Hospital in Putian, China and commissioning recently. The AB-BNCT device utilizes a linear radio frequency quadrupole (RFQ) accelerator to accelerate the proton beam, with an energy of 2.6 MeV and high current, for neutron generation via ^{7}Li(p,n)^{7}Be reaction, using a rotating water-cooled solid lithium (Li) target. A well-designed beam shaping assembly (BSA) is employed to produce good quality epithermal neutron beam suitable for cancer treatment. The BSA is composed of a magnesium fluoride (MgF_2) moderator with a thickness of ~ 25 cm, a lead reflector and a cylindrical cone-shaped collimator. The collimator mainly consists of lead and boron-containing polyethylene (~ 15wt% ^{nat}B) This device is currently operating with an average current of 12 mA. It is concluded from the experimental results that these detectors can be reliable tools for the QA of BNCT treatment beams. The detectors will be used as one of QA tools for the AB-BNCT device developed by Lanzhou University in the future.

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Keywords: Epithermal neutron flux detector, BNCT

Energy estimating track detector for precise neutron dose measurement of whole-body exposure during BNCT

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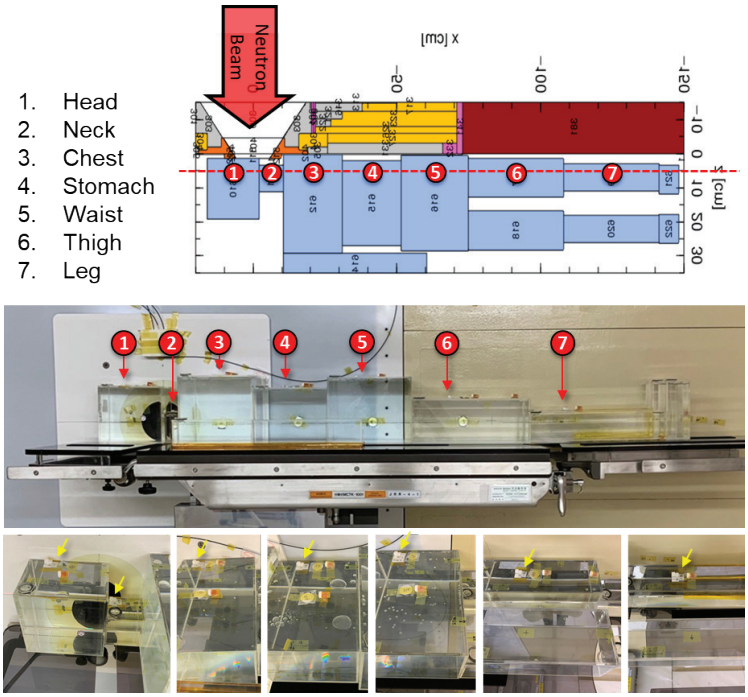

Figure captions: Fig. 1. Irradiation diagram.

Boron neutron capture therapy (BNCT) is a tumor-targeting radiotherapy based on the nuclear capture and fission reactions between thermal/epi-thermal neutrons and the boron-10 isotopes biochemically accumulated in tumor cells. During BNCT, not only tumor tissues but also patient body outside an irradiation field are exposed to neutrons. Furthermore, neutron energy spectra are significantly different for the positions of the body or the irradiation room [1]. Therefore, to monitor neutron exposure in BNCT, a wearable energy estimating detector is needed. In this study, CR-39 plastic nuclear track detector, a well-established detector for individual monitoring, was modified to apply to dose measurement at BNCT. A poly allyl diglycol carbonate plastic, commonly called for CR-39, was cut into small pieces of 1.57 x 9.5 x 0.87 mm as a detector [2]. The detector was used as a neutron dosimeter combined with neutron converters since a number of the tracks derived from neutron-induced charged particles are proportional to an exposed neutron dose. First, the detector was combined with two types of converters: boron nitride (BN) contained Teflon for detecting thermal/epi-thermal neutrons via nuclear capture reaction, and high density polyethylene (HDPE) for detecting fast neutrons via (n,p) reactions. In the next, two more converters were combined: 100% BN to estimate thermal rate in a BNCT beam in comparison with the BN contained Teflon converter, and 100% Teflon to be uses as a control dosimeter while avoiding the effect of the neutron-induced protons in the air. The design of the dosimeter including the thicknesses and densities of the converters were optimized by Monte Carlo simulation using PHITS code [3]. To verify the applicability of the developed dosimeter, several Irradiations with neutron beams were performed at iBNCT (Ibaraki BNCT, Tokai, Japan). The dosimeters were attached on top or side of a whole-body phantom filled with water at each position: head, neck, chest, stomach, waist, thigh, and leg (see Fig. 1). Beam conditions were 8 MeV protons with the current around 1.9 mA for almost 1 h irradiation. After those, the CR-39 detectors in the dosimeters were chemically processed to generate tracks on their surfaces. The processed detectors were scanned by a dedicated reader to obtain track densities. Neutron doses for epi-thermal neutrons or fast neutrons were determined by multiplying obtained track densities [mm-2 mSv-1] with each calibration factor. Moreover, the effective energies were estimated by the rate of the track densities between under BN contained Teflon converters and under 100% BN converters. Detailed results will be provided in the poster presentation.

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Keywords: Track detector, neutron dosimeter

S2P5

A multi-beam approach towards a high yield neutron source: enabling advances in non-clinical Boron Neutron Capture Therapy (BNCT) research.

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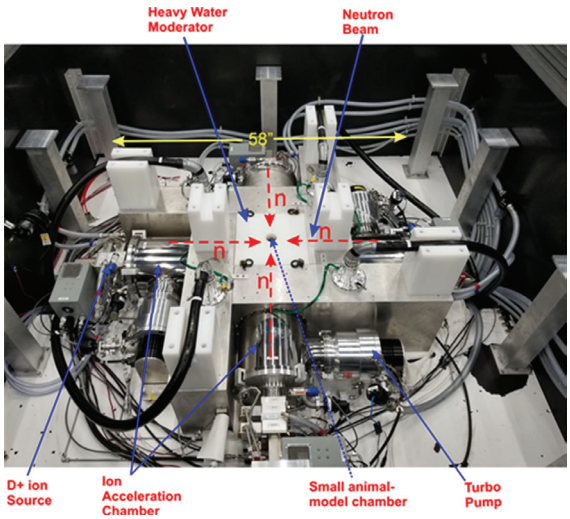

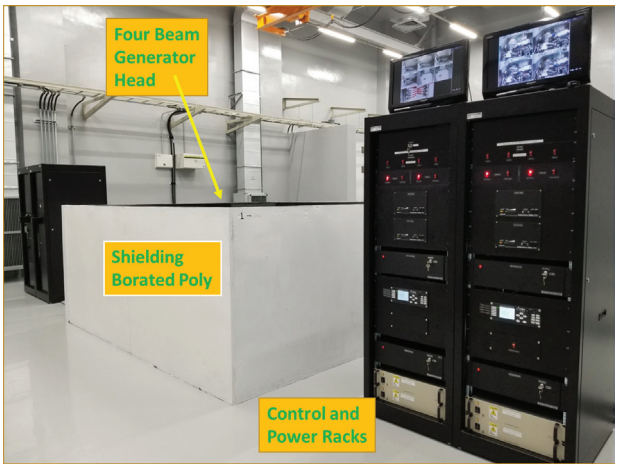

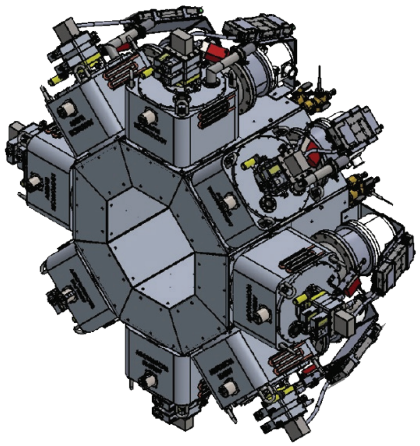

Figure captions: Images of the multi-beam neutron generator system with its shielding and electronic controls inside a testing facility; 3D rendering of an eight-beam system.

Traditionally, Boron Neutron Capture Therapy (BNCT) research has been carried out at facilities that utilize either MeV linear accelerators or nuclear reactors to generate neutrons. The cost of these facilities has generally prevented many individual contributors or principal investigators from advancing novel BNCT ideas/research. Historically, DD-fusion neutron generators have suffered from insufficient fast neutron yields for clinical applications and a lack of integrated moderation for high flux thermal neutrons. However, the size and cost of these neutron generators provide an attractive platform to support research done by small laboratories. Here, we propose a novel multi-beam approach of combining several neutron generators with integrated moderators to increase thermal neutron yield sufficient for new boron delivery drug research and non-clinical test studies. A multi-beam high flux thermal neutron source has been designed, fabricated, and tested. The neutron generators are arranged concentrically around the moderator and its central chamber. This maximizes the thermal flux at the central chamber while also reducing the unwanted components of x-ray, gamma, and fast neutrons. The moderator has been designed to produce an optimized thermal flux of neutrons obtained from four high-yield, DD-fusion neutron generators. The moderator has a central chamber wherein the small animal model or test phantom can be inserted and quickly removed. The moderator uses high density polyethylene (HDPE) and heavy water (D2O) to moderate the 2.5 MeV fast neutrons coming from the four DD-fusion generators. The four-beam system's maximum fast neutron (2.5 MeV) yield has been measured to be 8 x 10^10 n/sec, while its thermal (< 0.5 eV) flux is expected to be 2.6 x 10^7 n/cm2sec. The total supplied power is approximately 20 KW. The four generators plus moderator are enclosed in a 3 x 3 x 1.3 m shielded box; thus, such a system can be easily installed in small laboratories. Higher yields can be obtained by adding additional neutron sources.

Keywords: BNCT, thermal, compact, neutron source

S2P6

2D spatial distributions and uniformity of the H2 neutron beam at different distances from the lid

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Introduction
In the MARIA nuclear research reactor, a facility for irradiation in a beam of thermal and, in the future, epithermal neutrons is being built. The H2 horizontal channel will be used for radiobiological and materials research, development of mixed radiation field dosimetry, etc. As one of the stages of beam characterization, a two-dimensional scanning of the beam profiles was performed. The scans obtained for different positions allow to determine the radiation distribution in and around the beam axis along the entire length of the irradiation room.

Methods
A system of two linear guides was designed and manufactured for the positioning and automatic movement of a pair of gas detectors. The system is portable and allows to scan an area of 85 x 40 cm in one step. A pair of cylindrical ionization chambers with a volume of 7.4 cm3 and external dimensions of the active area ø 18.5 mm and 85.5 mm height were used as radiation detectors. The paired chambers allow separation of gamma and neutron components in the total tissue kerma rate. During the movement of the detectors and the simultaneous measurement of the radiation, the monitoring of the radiation stability in connection with the fluctuations of the thermal power of the reactor was realized.

Results
A series of beam profile scans were performed: for the reactor in the off-state and operating at nominal power, for different configurations of the beam shaping system (intermediate channel, beam shutter), at different distances from the surface of the H2 channel lid. The spatial distribution of the tissue kerma and the contribution of the neutron and gamma components were obtained. The values of the kerma rates in the beam axis at different distances were up to 15 Gy/h. The proportion of the neutron component of the kerma power in and around the beam axis varies widely, ranging from a few percent to tens of percent.

Conclusion
An efficient method for fast beam dosimetry and detailed profile scanning is manufactured, tested and implemented. The measurements performed confirm the correctness of the proposed measurement techniques and give good results that allow a reliable preparation and execution of experiments on the H2 channel beam of the MARIA reactor.

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Keywords: BNCT, neutron beam, neutron dosimetry

S2P7

A feasibility study on a small electron linear accelerator-based beam shaping assembly for boron neutron capture therapy

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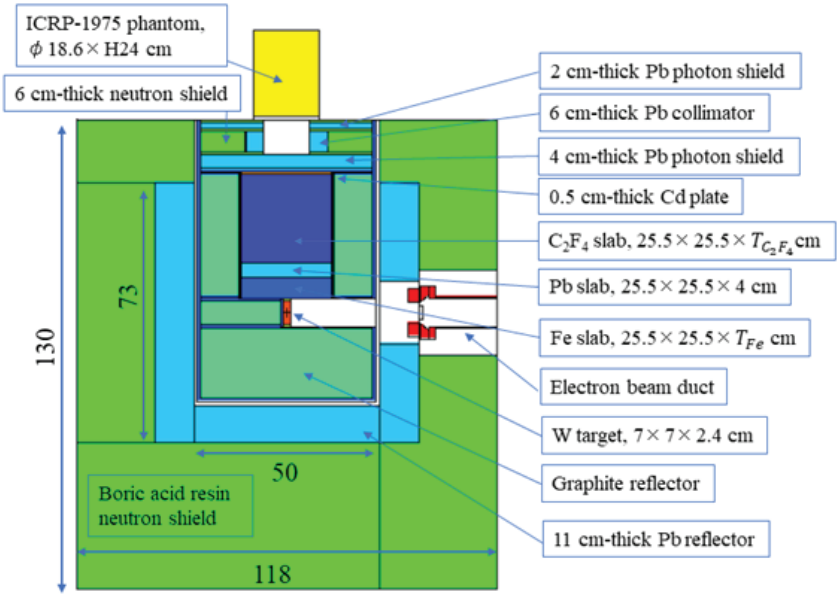

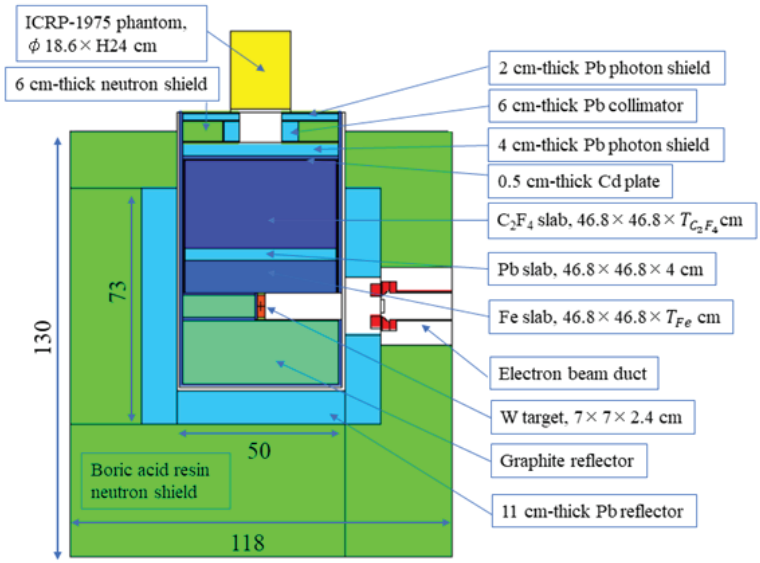

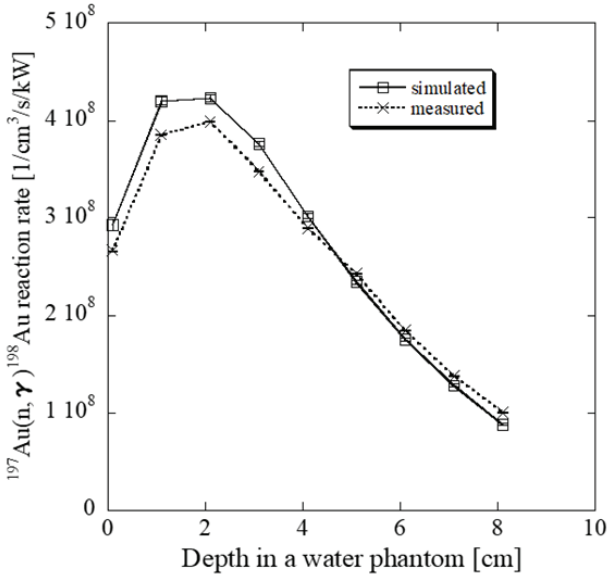

Figure captions:
Fig.1. An experimental BSA model for in-phantom dose calculations
Fig.2. A high-performance BSA model for in-phantom dose calculations
Fig.3. Comparison between measured and simulated reaction rate

As for the neutron source for beam shaping assemblies (BSAs) for AB-BNCT, a lithium or beryllium target driven by protons of 2.6 or 30-MeV, respectively, have been adopted. Both these targets are driven by proton beams with a beam power of more than 30-kW. A tungsten target driven by a 30-kW beam of 30-MeV electrons with an electron linear accelerator (LINAC) will create photo-neutrons adequate for AB-BNCT (Hiraga, 2020), and will have not only an advantage of a longer lifespan compared to a lithium target driven by a 30-kW beam of 2.6-MeV protons with an electrostatic accelerator but also an advantage of being cheaper than a beryllium target driven by a 30-kW beam of 30-MeV protons with a cyclotron. LINACs with a low beam power are desirable to improve the acceptability in hospitals, because a low beam power of electrons should reduce the cost of manu-

facturing LINACs. We therefore considered whether a BSA equipped with a tungsten target driven by a 15-kW beam of 33-MeV electrons of a small LINAC can deliver effective doses to deep seated lesions in tolerable irradiation times. We designed two types of BSAs, with the dimensions of important components for the BSAs as parameters. The one was an experimental BSA (Fig.1), and the other was a high-performance BSA (Fig.2) which had a larger neutron moderator and a larger fast-neutron filter than those of the experimental BSA. The experimental BSA was constructed, and the neutron measurement experiment with the experimental BSA was carried out to confirm the properties of the high-performance BSA. Simulation calculations using MCNPX were carried out to estimate the tumor and normal-tissue dose rate in a phantom exposed to a beam of the high-performance BSA, when the ^{10}B density in tumor and normal-tissue was 65 and 18 ppm, which should be achieved by the use of a boronophenylalanine for a boron carrier. With a limit on the peak normal-tissue dose of 10 Gy-eq, the advantage depth and the irradiation time of a beam were estimated at 8.3-cm and 3421 s, respectively. The advantage depth must be at least 8-cm to irradiate a lesion at the midline of the average-sized head (Binns, 2005), and the irradiation time should not exceed 1 h (IAEA, 2001). The calculation results on a beam of the high-performance BSA met these requirements.

The neutron measurement experiment was carried out by the use of the Hokkaido University LINAC that creates a 0.3-kW beam of 33-MeV electrons. A beam of the experimental BSA was irradiated to the nine pieces of gold leaf, which were placed on the axis of a water phantom at intervals of 1-cm, in five hours. The induced radioactivity in the gold leaf was measured, and the ^{197}Au (n,γ) ^{198}Au reaction rate per initial electron beam power [cm^{-3} s^{-1} kW^{-1}] was calculated from the induced radioactivity. Simulation calculations using MCNPX were also carried out to estimate the ^{197}Au (n,γ) ^{198}Au reaction rate [cm^{-3} s^{-1} kW^{-1}] in the gold leaf. The discrepancies in the simulated and measured data did not exceed 10 % (Fig.3). This result proves that simulation calculations provide a proper estimate for the neutron dose in a phantom exposed to a beam of the experimental BSA, and confirms that a beam of the high-performance BSA may deliver effective doses to lesions seated at the brain midline in tolerable irradiation times when a boronophenylalanine is adopted.

(This work was supported by JSPS KAKENHI Grant Number JP20K05378.)

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Keywords: Advantage depth, Irradiation time

S2P8

Design study on the angle and energy differential neutron spectrum for accelerator based BNCT

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Recently, accelerator-based neutron sources (ABNS) have been developed for BNCT instead of nuclear reactors. Generally, the neutron energy spectrum in the irradiation field created by an ABNS strongly depends on the design of the ABNS. In addition, the spectral characteristics vary depending on the angle of irradiation from neutron beam port. On the other hand, the irradiated dose highly depends on the neutron energy spectrum. Therefore, it is very important to measure the neutron spectrum in the treatment room, and it is also desirable to measure the neutron spectrum as an angular or spatial distribution to accurately evaluate the patients' whole body dose. To address this issue, we are developing a new neutron spectrometer, based on the "liquid moderator based neutron spectrometer" developed in the previous study [1]. This spectrometer can measure neutrons in a specific direction, and it is expected to be able to measure the angular distribution of the neutron energy spectrum, namely double (angle and energy) differential neutron spectrum, by performing the measurements at various detection angles. Since the previous spectrometer is overly sensitive to neutrons incident on the side surface of the detector, especially in cases with large measurement angles, we have attempted to develop a new spectrometer that can suppress unwanted neutron signal counts. In this study, a design study was conducted to investigate the possibility of measuring the double differential neutron spectrum in the epithermal neutron field irradiated by ABNS. A design study for a new spectrometer was carried out using MCNP-6. This spectrometer employed a ^{3}He proportional counter as a neutron detection element, and cylindrical neutron shield was installed surrounding the counter. To measure the neutron spectrum, $NaBF_4$ solution was installed in the direction of neutron incidence as a moderator, with a thickness that could be continuously controlled. An optimized design for the surrounding neutron shield was investigated, aiming to improve the sensitivity to desired neutrons passing through the liquid neutron moderator. The signal count rate was calculated based on the ^{3}He(n,p)^{3}H reaction rate in the ^{3}He proportional counter, considering two neutron irradiation models: one irradiating the neutron field parallel to the detector axis for response function calculation, and the other at a 60-degree angle from the detector axis, considered as the maximum measurement angle in real conditions, to evaluate the shielding performance against the side-incident neutrons. After the design study, we will perform a numerical simulation to investigate the feasibility of measuring the double differential neutron spectrum, using an epithermal neutron field generator with a DT neutron source [2].

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Keywords: ABNS, neutron spectrometer, angular distribution

S2P9

Beam emittance measurement of low energy H− ion beam via solenoid scan method on the injector of AB-BNCT

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The Korea Institute of Radiological & Medical Sciences (KIRAMS) designed and constructed the injector test stand (ITS) for electrostatic accelerator-based boron neutron capture therapy (AB-BNCT), the so-called KIRAMS boron neutron capturetherapy electrostatic tandem accelerator. To generate neutrons for BNCT, the accelerated energy of the proton beam, which reaches 2.4 MeV, is projected onto the lithium target. As a tandem electrostatic accelerator, a gas-type stripper is installed in the middle of the accelerator system. As an initial particle, a negative hydrogen ion beam with a high current reaching 15 mA is required, and it is critical to transport the ion beam to the entrance of the electrostatic accelerator so that it is precisely matched without beam loss. To fulfill this requirement, an ITS system was fabricated and commissioned. The ITS component consists of a 30 keV negative hydrogen ion (H−) source, a solenoid magnet, and a beam profile monitor (BPrM). The main purpose of the ITS is to obtain a full understanding of the high-current H− ion beams. In general, to measure the characteristic parameters in high-current and low-energy ion beams, the beam spread due to space charge effect which is a repulsive force between charges of the same type must be considered. The charged particle beams rotate and focus in the solenoid magnet and can be described in matrix notation. By changing the solenoid magnet strength and measuring a beam profile at BPrM the Twiss parameters, including the transverse beam emittance at the entrance of solenoid, were measured considering the space charge effect at a level of mA beam current. To determine whether the space charge effect itself is dominant or not, track simulations with and without applying the space effect were conducted and compared with real data. The various performence for the beam emittance measurement at the entrance of solenoid by using the linear matrix formalism will be presented and the results will be compared with the one of simulation.

Keywords: solenoid, Injector, emittance, space, charge

S2P10

Development of a compact Beam shaping assembly for Boron Neutron Capture Therapy treatment of Pontine Glioma.

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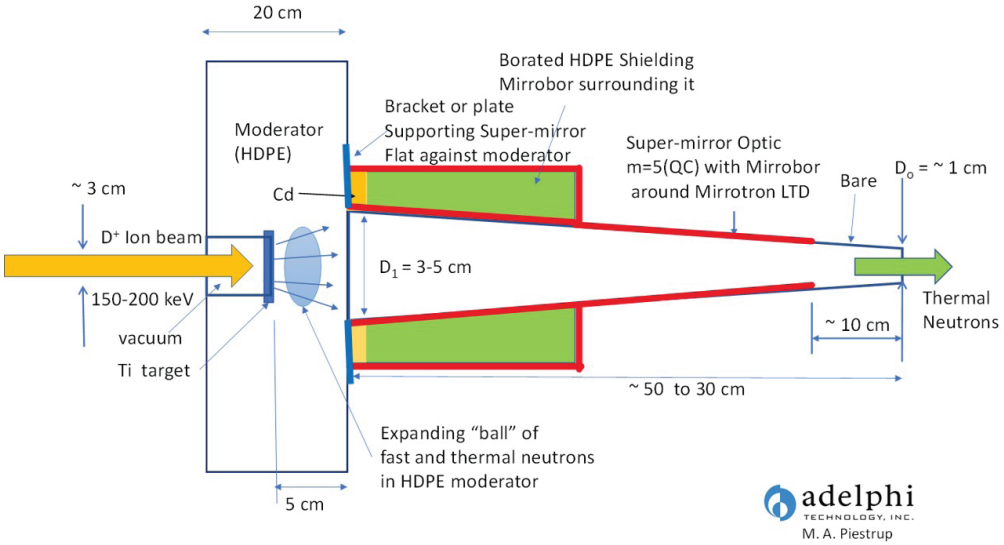

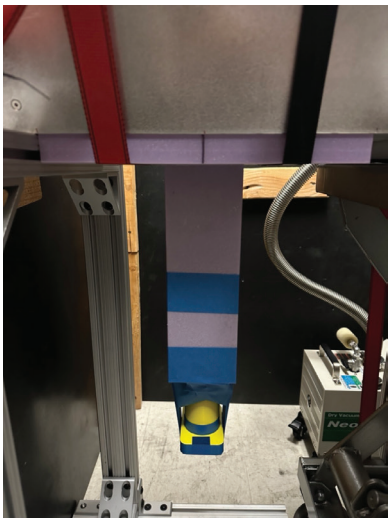

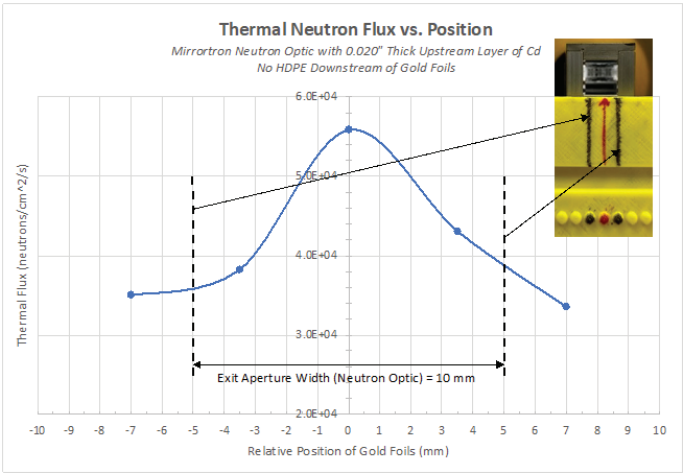

Figure captions: Pontine BSA positioned under the pre-moderated neutron generator and its measured thermal neutron flux.

Approximately 150-300 patients are diagnosed with DIPG in the USA per year with the median age of approximately 6-7 years old and the median survival range of 8-11 months. Conventional radiation therapy is palliative adding a few months to the child's life. A more targeted method is to increase cancer cell death by Boron Neutron Capture Therapy (BNCT). We propose using a compact neutron source with a collimator and robot arm, to be developed, that permits radiation to go directly to the cancer site while minimizing the dose to healthy tissue. In conventional radiation therapy, the main palliative treatment for DIPG, both healthy and cancerous cells receive roughly the same dose. This temporarily slows the tumor growth, but radiation treatments must be discontinued to limit healthy tissue damage. BNCT can provide targeted destruction of the cancer cells while minimizing healthy tissue damage. A compact generator coupled to a neutron optic can deliver the neutrons directly to the pons and, with a precise boron delivery, targeted cancer cells can be destroyed. To provide a more directional tumor-volume and cell-specific targeting we propose using a compact neutron generator integrated with a spectral- and volume-shaping delivery optic to direct thermal neutrons to the pons inside the body with minimal invasiveness. The ratio of the boron delivered to the cancer cells vs that taken up by healthy cells increases the cancer cell death by roughly the same ratio. The major component of our program is an Adelphi proprietary high yield neutron generator, with an internal moderator that slows down neutrons to thermal energies. This is done by using a high-density polyethylene moderator which is in contact with the neutron emitting titanium target. To this moderator we attach a beam shaping assembly (BSA) that focuses, shapes, and filters the neutron beam so that its thermal neutron content can be directed to the cancer site. The neutrons are captured by boron atoms that have been absorbed by cancer cells. The boron atoms absorb the thermal neutron and then fission emitting charged and energetic Li and alpha particles that strike cancer cells' DNA killing it.

Keywords: beam shaping assembly, pontine glioma

S2P11

Considerations of Surface Guided Boron Neutron Capture Therapy: Combining A More Flexible Patient Position Method with NeuMANTA

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Abstract
Boron neutron capture therapy (BNCT) is a promising radiation therapy technique that uses neutron beams to selectively irradiate tumor cells by capturing boron-10 nuclei. Accurate patient positioning is crucial for ensuring effective treatment and minimizing damage to surrounding healthy tissues. In YBNCT-2022, a new patient position method that is base on laser and 3-markers was introduced and implemented by Neuboron for real treatment practice. However, this method was found to be time-consuming when used to align markers with lasers. To address this issue, a more flexible patient position method, known as the surface guided patient position method, was proposed. This method utilizes advanced imaging technologies, such as optical surface imaging or stereoscopic imaging, to create a 3D surface image of the patient's body, which is then compared to reference data in the treatment plan to accurately position the patient using a robot system. While surface guided radiation therapy (SGRT) is mentioned in conventional radiation therapy, it is not commonly used in clinical applications, except for quality assurance, as the amount of data collected by this method is typically unnecessary. However, for BNCT, the patient position process presents an entirely different workflow, with the need to move the patient instead of adjusting the beam position. Therefore, the surface guided patient position system has the potential to improve both the precision and efficiency of BNCT.

1. Accurate and fast patient position
Advanced imaging technologies typically offer accuracy within the submillimeter range. This precision can be utilized to accurately position patients for treatment based on surface markers or imaging. Furthermore, the treatment planning system can be seamlessly integrated into this method, allowing for automatic acquisition of position data. This integration accelerates the positioning process and prevents the risk of human error.

2. Real-time monitoring and feedback
The BNCT treatment process usually lasts about 30 minutes. During the treatment, the patient lies on a couch while a neutron beam is directed towards the targeted area. Any movement by the patient can impact the final dose. A surface-guided patient position system continuously monitors the patient's body surface, captures high-resolution images, and tracks the position of markers placed on the patient's skin. This captured information is processed in real-time, enabling the system to assess and adjust the patient's position as necessary throughout the treatment delivery.

3. Improved patient comfort
In BNCT treatment practice, the patient's position is determined, and they are permitted to rotate around the beam center without affecting the final dose distribution. The implementation of a surface guided patient position system can offer methods to assist the patient in finding a more comfortable position. This approach has the potential to enhance patient compliance and cooperation during treatment, consequently improving treatment accuracy.

Keywords: bnct, surface guided, patient position

S2P12

The co-research project with CNEA for an in-air electrostatic accelerator based BNCT in KIRAMS

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In 2019, KIRAMS initiated a project to acquire in-air electrostatic accelerator technology from Argentina's National Atomic Energy Commission (CNEA). The project's ultimate goal was to construct a 1.5 MeV/30 mA deuteron accelerator for Boron Neutron Capture Therapy (BNCT). Due to space constraints, the project began with the construction of a 240 keV single-ended electrostatic proton accelerator. Unfortunately, the COVID-19 pandemic caused project delays. KIRAMS manufactured the basic structure, while core components like the high-voltage power supply, electrostatic acceleration tube & quadrupole, and the associated high-voltage engineering techniques and know-how for maintenance and commissioning were imported from Argentina. The ion source used was a negative filament D-pace type. CNEA provided on-site support during the construction and commissioning of the accelerator through three separate visits to KIRAMS. In late 2019, essential components arrived at KIRAMS, including the acceleration tube, matching tube, electrostatic quadrupoles, chambers, and aluminum target. The following year, our team in KIRAMS successfully manufactured the basic support structure for the accelerator and a unique high-voltage dome-shaped potential chamber capable of sustaining 750 kV in an air environment. In 2021, a team of three technicians from Argentina spent two weeks at KIRAMS constructing the basic structures and vacuum system. A second team comprising one technician and two engineers followed in mid-2022, focusing on high-voltage engineering and the control system. During this visit, minor issues were identified with high-voltage devices and structural parts, necessitating replacements. Late 2022 saw the arrival of two engineers to address these issues. They successfully replaced the high-voltage potential support components and certain portions of the power supply. A two-week commissioning process then took place, culminating in the successful acceleration of a 10 mA H- beam to 240 keV in December 2022. This single-ended electrostatic accelerator utilizes vertically stacked stages. Each stage possesses a specific voltage potential and progressively increasing potential with saperated power supplies. The beam position was monitored through a view window using a wireless camera. Notably, a series of electrostatic quadrupoles (ESQs) enabled focusing and guiding the high-current ions along the acceleration path without additional beam optic devices, contributing to the accelerator's efficient operation. However, limited space at KIRAMS remains a significant challenge, necessitating a more compact accelerator solution. Despite the project's achievements, the decision was made to halt it in favor of developing a newly designed, high-current tandem accelerator with a smaller footprint.

Keywords: accelerator, in-air, electrostatic, deuteron, proton

S2P13

Developing a high current/low energy tandem accelerator for AB-BNCT in KIRAMS

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In 2018 KIRAMS (Korea Institute of Radiological & Medical Sciences) decided to start developing an accelerator for AB-BNCT. Cyclotron was considered for the very first model. A conceptual design of a 10 MeV cyclotron which had structure of two cyclotrons stacked horizontally was proposed to increase the beam current. But the size of these two stacked structures was not dramatically smaller than 30 MeV cyclotron. The radiation safety was also an issue. After a conceptual study, high current/low energy electrostatic accelerator was chosen as the final model for AB-BNCT. KIRAMS decided to transfer the electrostatic accelerator technology from CNEA, Argentina for fast-track. But as soon as the co-research project started COVID-19 pandemic began and the project was delayed. In the meantime, KIRAMS start to develop a high-current tandem accelerator. The first prototype was 500 keV proton tandem accelerator. The H- ions was extract from ion source with energy of 30 keV. Through an Einzel lens and a solenoid magnet the initial proton beam was focused to the first acceleration tube. It has 60 potential gaps to 250 kV high voltage terminal and connected to high voltage terminal. In the high voltage terminal, an Ar gas stripping tube with a diameter of 15 mm and 400 mm in length was installed. Turbomolecular pumps were install for each side at entrance and exit of the stripping tube for hydrogen ion beam. These two pumps recirculate the Ar gas to the middle of the stripping tube. The devices need cooling in the high voltage terminal, including stripping tube, was cooled by FC-3263 (3M) instead of deionized water. The proton (H+) beam which pass through the stripping tube injected to the second acceleration tube. This tube was installed after the high voltage deck and maintain high voltage potential from 250 kV to 0 kV (ground level). The focusing and steering of high current ion beam was the main issue. The alignment of the accelerator from ion source to the second acceleration tube was conducted with a precision of ±0.2 mm. The accelerator had two steering magnets in series, but the entrance of the stripping tube melted down two times. Additional process was performed to compensate the basic alignment process. During irradiate the beam only with focusing components the accelerator aligned once again by moving the injector mechanically which is the region from ion source to solenoid magnet. After doing this additional process, the beam tunning process was easier. As a result, we could successfully accelerate 6 mA of proton to the energy of 500 keV through the narrow stripping tube. Now KIRAMS is on the last stage of developing a 1.2 MV/ 40 mA power supply and a 2.4 MeV tandem accelerator is under construction. In this year, we plan to accelerate high current beam of 1.5 MeV first before performing the full energy.

Keywords: High-current, tandem, AB-BNCT

S2P14

Design of Beam Shape Assembly for 2.4 MeV electrostatic tandem accelerator based neutron source for Boron Neutron Capture Therapy : Monte carlo study

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Boron Neutron Capture Therapy (BNCT) exploits the high neutron capture reactivity of boron-10 for cancer treatment. Neutron capture reactions between neutrons and boron-10 generate alpha particles and lithium particles, which travel a very short distance (~10 um) within the body, transferring their energy and theoretically enabling the selective elimination of cancer cells without affecting normal cells. This treatment method is anticipated to significantly impact lesions such as glioblastoma, head and neck cancer, recurrent head and neck cancer, melanoma and others. A crucial aspect of BNCT involves securing high-quality epithermal neutron sources (0.5 eV to 10 keV). Various types of accelerator-based neutron sources are actively studied globally to obtain high-quality neutron sources. Depending on the type and energy of the accelerated particle, various targets such as lithium and beryllium are employed to generate neutrons. However, neutron sources utilizing accelerators have relatively high energy, necessitating the reduction of the energy range of generated neutrons. The Beam Shape Assembly (BSA) is designed to decrease neutron energy from relatively high levels to an energy range advantageous for neutron capture reactions, serving as an essential component of an accelerator-based BNCT treatment system. The specifications of BSA vary depending on the energy of neutrons generated in the reaction between accelerated particles and target. The performance of BSA is recommended by IAEA technical documents. The Korea Institute of Radiological and Medical Sciences (KIRAMS) is developing a BNCT system utilizing a 2.4 MeV proton electrostatic tandem accelerator with a lithium target. In this study, a BSA system was designed using MCNP (v6.2) for the 2.4 MeV proton accelerator-based neutron source. Lead (Pb), magnesium fluoride (MgF2), boron carbide (B4C) and tungsten(W) were used for the reflector, moderator, and collimator parts of the BSA, respectively. BSA performance was evaluated based on epithermal neutron flux, epithermal to thermal ratio, fast neutron contamination, and gamma contamination indicators. Additionally, neutron and gamma distributions were confirmed.

Keywords: BNCT, BSA, Monte-carlo, Lithium target

S2P15

Topology optimization of high-performance AB-BNCT moderators

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To use neutron fields for Boron Neutron Capture Therapy (BNCT), the energy of source neutrons must be reduced to approximately 10-20 keV, the limit of an epithermal neutron field, which is considered ideal for the treatment. To achieve this, a neutron moderator needs to be placed between the source and the patient. The design and optimization of this component has been the focus of numerous studies, with various design proposals published to date. However, all of these studies use a similar methodology, with optimization done through parametric approaches. These approaches involve using a limited number of geometric parameters (radii, lengths, thicknesses, etc.) and materials to describe the moderator parts. Each potential configuration is then simulated to identify the set of parameters that offer the best compromise in terms of the quality of treatment and the intensity of the neutron field generated at the moderator exit. Parametric approaches have been instrumental in identifying and constructing AB-BNCT moderators that perform well. These moderators can deliver treatment in less than an hour, with excellent penetration capacity into the treated tissues. However, current performance values of TD and AD (*) remain limited by human imagination, saturating at 7.6 cm and 10-11 cm, respectively. To surpass these limitations, it may be necessary to abandon the parametric approach and adopt a systematic approach called topological optimization (OptTop). This approach is widely used in scientific and engineering fields. In this approach, thousands or even millions of design parameters, including positions and materials, are optimized simultaneously, as opposed to only a few in the parametric approach. For this study, we optimized 92,000 parameters in total by optimizing each possible volume fraction (100) of each candidate material (4) in each voxel (230) of the moderators. Thanks to recent advancements in modern mathematics and the increase in available computing capacity, we were able to execute such an approach. Through the application of a multi-material and multi-constraint OptTop approach, we were able to create moderator designs with unmatched levels of performance. These designs achieve TDs of up to 10.2 cm, which is 30% higher than any previously recorded values. To achieve these levels of performance, the OptTop algorithm we developed generates complex structures that are beyond human imagination. These structures combine moderation bodies made of fluorinated materials and polyethylene with unique, counterintuitive shapes, along with neutron absorber components and neutron tunnels that mimic the effects of multi-directional treatment. We will showcase examples of these new types of moderators and their configurations, along with their performances. (*) The penetration capacity of the neutron field into the patient's tissues can be quantified by several FOMs, the most common of which for brain treatments being the Advantage Depth (AD) and the Treatment Depth (TD). These AD and TD are respectively the depths for which the dose delivered to the tumor tissues is still equal to 1 time (AD) or 2 times (TD) the maximum dose delivered to healthy brain tissues.

Keywords: neutron moderator, treatment depth, optimization

S2P16

Characterization of the neutron flux during irradiation of biological samples towards BNCT research in the MARIA Research Reactor using hydraulic rabbit system.

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One of the challenges when working with mixed radiation produced in the Research Reactor is the determination and characterization of the appropriate radiation components. Nuclear reactors generate gamma, beta, alpha and neutron radiation during operation. Due to the range of radiation in an aquatic environment, two components are important from the measurement point of view: gamma radiation and neutrons. Additionally, the neutrons available for experiments are characterized by different energies, which result from the nuclear processes taking place in the core and surroundings of the reactor core: fission, moderation, and scattering. As a result of these processes, the energy spectrum of available neutrons may change in time and space. This problem occurs, among others, in research on BNCT therapy, in which thermal neutrons are captured by B-10 atoms, as a result of the ongoing nuclear reaction, an alpha particle and a Li-7 nucleus are created. The probability of this reaction occurring is described by the microscopic cross-section, which depends on the energy of the molecule initiating the reaction, the neutron. At the MARIA Research Reactor, BNCT research is carried out using a hydraulic rabbit system, which allows samples to be introduced to the periphery of the reactor core during its operation. The irradiation time is measured with an accuracy of 1s. Due to its design, online methods cannot be used in hydraulical rabbit system. Samples introduced into the core area are packed in special irradiation containers. These containers are relatively small in size (internal diameter 23mm and available height 60mm). A important technological problem in such a case is the simultaneous monitoring of the neutron flux, with particular emphasis on the division into energy groups of neutrons present in the irradiation environment. The purpose of the research and calculations was to compare two available measurement and calculation methods to select the most accurate one for use in further work on BNCT. The research carried out used a new approach to neutron monitors previously used in Neutron Activation Analysis and the associated mathematical apparatus. In the new four-detector method, Au, Cr, Ni and Mo were selected. It involves the use of chemical elements evenly diluted in one detector, instead of the previously used method of two cut metal foils. It also does not require the use of a cadmium shield to determine the epithermal neutron component. The use of the new method is also associated with the introduction of new codes for calculating the stream based on the Hogdahl convention [1]. The use of the new approach allowed for better determination of neutron parameters during live cell irradiation experiments in a demanding hydraulic rabbit environment, the main feature of which is a limited volume.

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Keywords: neutron flux, BNCT, flux distribution

S2P17

PREDICTIVE ANALYTICS FOR SUSTAINABLE SUPPLY CHAIN MANAGEMENT

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Abstract:
In the dynamic landscape of contemporary business, the symbiotic relationship between predictive analytics and sustainable supply chain management (SSCM) emerges as a catalyst for transformative change. This abstract encapsulates the essence of a comprehensive exploration into the integration of predictive analytics within the realm of sustainable supply chain practices, delineating the critical intersections and implications for businesses navigating the complex terrain of global commerce.
The context of sustainable supply chain management is characterized by an evolving paradigm that extends beyond traditional economic considerations. The imperative to balance profitability with environmental and social responsibility has prompted organizations to seek innovative solutions. Predictive analytics, leveraging sophisticated data analysis techniques, emerges as a strategic enabler to address the multifaceted challenges inherent in the pursuit of sustainability within supply chains.
This research embarks on a journey to unravel the intricate relationship between predictive analytics and sustainable supply chain management. Grounded in a holistic understanding of SSCM, the study aims to assess the transformative potential of predictive analytics in enhancing decision-making processes, optimizing operational efficiency, and contributing to overarching sustainability goals.
The objectives of the study are multifaceted. Firstly, the research delves into the modeling of sustainability parameters, encompassing metrics such as carbon emissions, ethical sourcing practices, and social impact indicators. Through the incorporation of these parameters into predictive models, the study seeks to illuminate avenues for businesses to align their supply chain decisions with broader environmental and social imperatives. Secondly, the study explores the application of predictive analytics in demand forecasting, inventory management, and resource allocation. By harnessing historical data and leveraging advanced analytical techniques, the research aims to identify opportunities for minimizing waste, reducing excess inventory, and streamlining supply chain operations, thereby contributing to the economic and environmental sustainability of organizations.
The third dimension of inquiry revolves around risk mitigation and resilience within the supply chain. The study investigates how predictive analytics can play a pivotal role in identifying and mitigating risks associated with disruptions caused by natural disasters, geopolitical events, and market fluctuations. By enhancing the adaptive capacity of supply chains, organizations can fortify their resilience in the face of unforeseen challenges.
Additionally, the research scrutinizes the impact of predictive analytics on supplier relationship management. It explores how predictive insights foster collaboration, communication, and risk management across the supply chain network. The study posits that a data-driven approach can enhance the overall efficiency and effectiveness of supplier relationships, contributing to the sustainable practices of the entire supply chain ecosystem.
In essence, this research contributes to both academic discourse and practical application by unraveling the synergies between predictive analytics and sustainable supply chain management. As organizations increasingly recognize the intertwined nature of economic success and environmental stewardship, the findings of this study offer a roadmap for businesses to harmonize profit-driven objectives with responsible and sustainable supply chain practices. Through a holistic exploration of these critical intersections, this research advocates for the integration of predictive analytics as a strategic imperative in the pursuit of a resilient, responsible, and sustainable future for global commerce.

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Keywords: Predictive analytics, sustainable supply chain

S2P18

Optical monitoring of position and size of direct current particle beams

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Conventional position monitors for bunched charged particle beams cannot be used for direct current (DC) proton beams generated by electrostatic accelerators for neutron generation. Such DC beams with relatively high proton current may be monitored by light emission from atoms of the background gas excited by the beam. These same diagnostics may be applied to monitoring DC beams of negative ions, where light is emitted by the beam particles themselves.
A system of optical monitoring of proton beam position and size was developed for a neutron beam system (NBS) by TAE Technologies for boron neutron capture therapy (BNCT). The NBS is designed as a DC tandem accelerator with 150 keV injection of negative hydrogen ions and a beam delivery to up to three treatment rooms equipped with thin lithium targets to generate neutrons. Optical beam monitors are used on both the injection side of the tandem to monitor the negative hydrogen ion beam, and on the high energy beam lines to monitor the proton beam.
Monitoring the beam on the outlet of the tandem accelerator is done by registration of light emitted by gas outflow from the charge exchange target of the tandem. In the high vacuum, high energy beam line, a special pulsed gas puff system was designed to “illuminate” the beam while taking a snapshot image. Beam images in two perpendicular plane are acquired by a pair of high sensitivity cameras. An interpolated cross section of the beam is derived in real time to determine the shape, size, width and inclination. Light absorbing view dumps with fiducials are used to increase the contrast and to provide tools for precise positioning and scaling of the acquired images.
The low intensity images are processed by specially designed software, which performs preliminary real time image processing and then converts images of the preset regions of interest into beam cross section profiles. The profiles are further filtered to reduce the noise and then interpolated to obtain position of the center and the full width at half maximum of the beam. Shift of the beam position between areas of interest is used to calculate inclination of the beam. The optical beam monitoring system is able to acquire position of negative and positive beams with current from 1 mA with repetition rate up to 10 Hz. Spatial resolution of the system reached 0.1-0.2 mm, which is sufficient for the clinical needs of the NBS.

Keywords: optical monitoring, proton beam, tandem

S2P19

Study of the out-of-field dose from an accelerator-based neutron source for boron neutron capture therapy

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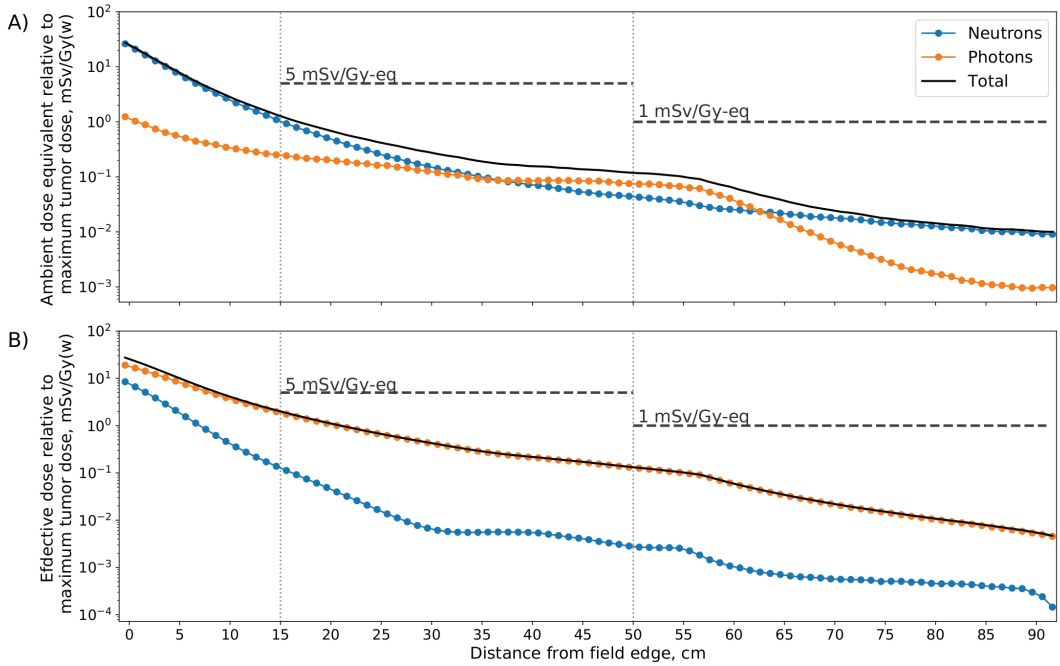

Figure captions: Figure 1. A) Ambient dose equivalent for air cylindrical rings. B) Effective dose normalized for cylindrical rings.

One important issue in Boron Neutron Capture Therapy is the delivered dose to the tissues surrounding the target tumor. To address this concern, an international recognized standard for light ion beam systems sets two recommended limits for out-of-field dose based on distance from the field edge. According to these standards, the maximum absorbed dose from all radiation types shall not exceed 0.5 % of the maximum dose at distances 15 cm to 50 cm from the field edge. As one moves beyond the 50cm threshold (distances>50 cm) from the field edge, an even more stringent criterion comes into play, mandating that the maximum absorbed dose shall not exceed 0.1 %.

This work is a continuation of our previous works focused on the design of an accelerator-based neutron source for BNCT. We have successfully developed an innovative Beam Shape Assembly (BSA) [1] that adheres to the criteria set by the International Atomic Energy Agency (IAEA) [2] for BNCT treatments. The neutron production of this beam is based on the reaction of a 30 mA proton beam on a lithium-7 target [3] at energies up to 2.1 MeV, a lower energy than the rest of options considered in the literature, with the consequent reduction of the maximum energy of the fast neutrons produced. Using this BSA, in the present work, we characterize by Monte Carlo simulations the dose outside the neutron field, using the designed BSA as the focal point or source.

The out-of-field dose has been evaluated by estimating ambient and effective dose parameters. Additionally, a detailed analysis of the dose effect of the boron uptake in healthy tissues has been conducted to enhance the computation of the effective dose, as we can see in Figure 1. This dual-focused methodology offers a comprehensive insight into radiation exposure beyond the treatment area, encompassing both overall ambient dose and the influence of boron distribution in healthy tissues. These calculations play a crucial role in enhancing the precision of effective dose computations and advancing our understanding in the realms of radiation safety and therapeutic efficacy.

In conclusion our design for a future accelerator-based source for BNCT meets adequately well the criteria defined from other forms of radiotherapy on both equivalent and effective dose outside the field.

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Keywords: BNCT, neutrons, out-of-field, effective dose,

S2P20

Evaluation of thermal neutron flux and gamma-ray dose rate inside PMMA phantom

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In recent years, accelerator-based BNCT (AB-BNCT) facilities have increased. The structure of a beam-shaping assembly varies depending on the combination of accelerators and target materials, and the neutron spectra irradiated to patients are vary as well. To develop AB-BNCT as a general treatment, an unified measurement method that can be used globally must be established. To conduct a quality assurance (QA) of the BNCT procedure, a thermal neutron flux and gamma-ray dose rate inside a water phantom have been measured. Neutrons used in BNCT have wide range of energies, but we focused on the thermal neutron, which is the main component for QA. However, in the measurements using the water phantom, conditions such as water temprature and quality vary depending on the day and facility. In this study, we selected a polymethyl methacrylate (PMMA) phantom. The same PMMA phantom can be used to perform irradiation tests at different facilities to evaluate the characteristics of each irradiation field. The thermal neutron flux was measured via a gold activation method using gold foil, and gamma-ray dose rate was measured by a thermo-luminescence dosimeter (TLD). Irradiation tests were performed at Cyclotron-Based Epithermal Neutron Source (C-BENS) in Kyoto University. The PMMA phantom measured 30×30×30 cm^3 and featured a density of 1.20 g/cm^3. To measure the thermal neutron flux and gamma-ray dose rate, the gold foils and TLDs were placed along the central beam axis inside the phantom, respectively. Experimental results were compared with simulations calculated by PHITS (ver. 3.28). To calculate the thermal neutron flux, a thermal neutron scattering law (TSL) for the phantom material should be considered. TSL data from JENDL-5 were used. We also simulated the thermal neutron disritbusion that the density was changed to 1.15 and 1.25 g/cm^3, because the density was different depending on the manufacturers. The thermal neutron flux inside the PMMA phantom was about 8 % lower than the water phantom at a depth of 2 cm, whereas it was about 40 % higher at 15 cm owing to the lower hydrogen density of PMMA compared with that of water. The gamma-ray dose rate inside the PMMA phantom was lower than that in the water phantom. The experimental and simulated results showed good agreement. When the density of the PMMA phantom was changed by ±0.05 g/cm^3, the thermal neutron flux at a depth of 2 cm and 15 cm were changed by ±3 % and ±15 %, respectively; thus, the difference generated by the density was increased as the depth increased. In conclusion, irradiation tests using the PMMA phantom were performed, and the distributions of the thermal neutron flux and gamma-ray dose rate were measured through experiments and simulations. In the future, the same irradiation tests will be conducted at different AB-BNCT facilities.

Keywords: phantom, neutron, gamma-ray

S2P21

Development of a microdosimetry-based assessment method with the boron distribution for the evaluation of biological effectiveness in BNCT irradiation field

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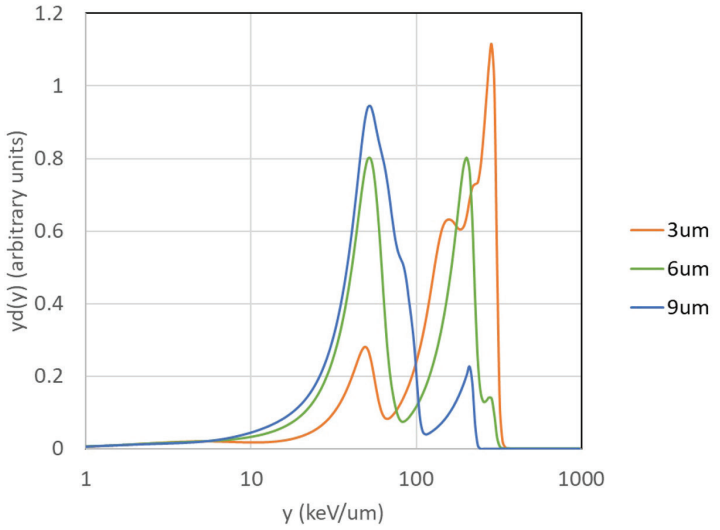

Figure 1 Microdosimetric d(y) distribution inside the nucleus with ^{10}B located at 3, 6, and 9 μm away when irradiated with thermal neutrons.

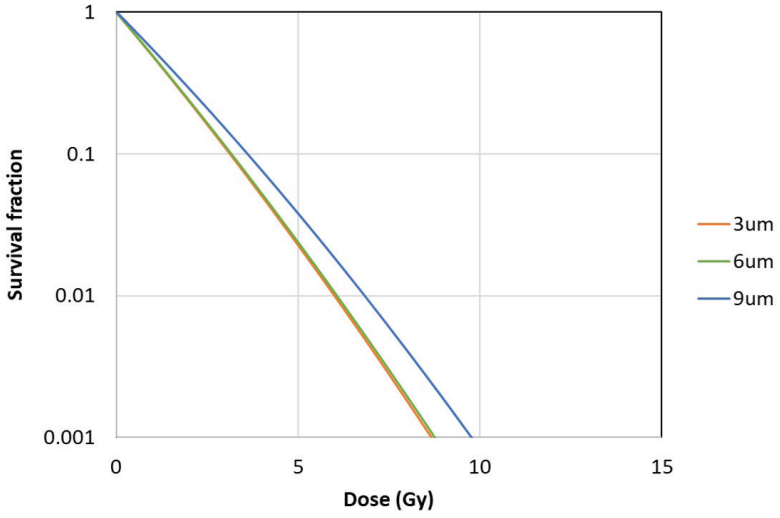

Figure 2 Survival curve derived from the yd(y) distribution and the MK model

[Introduction] Currently, fixed values of Relative Biological Effectiveness (RBE) and Compound Biological Effectiveness (CBE) are utilized in BNCT treatment planning. It is desired a more accurate dosimetry that considers the neutron energy spectrum and the boron (^{10}B) distribution at each evaluation position. Accurate determination of the RBE with neutron energy spectrum and CBE with the ^{10}B distribution in cellular size level is crucial for precise dose calculations, leading to a more effective treatment planning. Additionally, optimizing the distribution of boron agents holds promise for developing superior agents, thereby enhancing the therapeutic efficacy of BNCT. Despite BNCT becoming an approved treatment modality, a calculation method for accurately determining RBE and CBE, and establishment of a model in the treatment planning system has not yet been established. Therefore, our group is attempting to use the PHITS Monte Carlo simulation code and the microdosimetric kinetic (MK) model[1]to derive cell survival rates using ^{10}B distributions for calculation of accurately determining RBE and CBE.

[Material and Method] The effect of the 10B distribution on the microdosimetric spectra inside a cell nucleus was evaluated using PHITS simulation. A spherical cell with 10B located at 3, 6 and 9 μm away from the nucleus (radius of 0.22 μm) was simulated. The T-SED tally was used to calculate the microdosimetric spectra in the cell nucleus. The parameters required to estimate the survival curves using the MK model were obtained from a previous study using the thermal neutron irradiation beam port at the JRR-4[2].

[Results and Discussion] The simulated microdosimetric spectrum yd(y) at the three different ^{10}B locations are shown in Fig.1. For the position of 3 and 6 μm cell, events at around several hundred keV/mm from the high LET particles produced at the ^{10}B location were mainly recorded, whereas these events were not recorded for the 9 μm radius. Fig. 2 shows the survival curves for the three different locations derived from the MK model parameters and the simulated microdosimetric spectra. The microdosimetric parameter were set to be 0.061Gy^{-1}, 0.011Gy^{-2}, 0.22 μm and 130keV /μm, respectively. From these results, it was found that the cell killing effect was large as the boron compound was located near the cell nuclei.

[Conclusion] We were able to determine the cell survival curve when boron was distributed at 3, 6, and 9 μm away from the nucleus using the PHITS T-SED tally and MK parameters derived from the experimental data. The results indicate that the location of the boron distribution in relation to the nucleus affects the cell survival rate. Although the current model is simplistic, our plans will include refining calculations using a more realistic cell model and expanding the methodology from the micro to the macro level.

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Keywords: BNCT, MK model

S2P22

A study on dose-component discrimination estimation methods using micellar gel dosimeters for quality assurance in boron neutron capture therapy

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$$\begin{pmatrix} k_{H,s} & k_{N,s} & k_{B,s} & k_{G,s} \\ k_{H,b} & k_{N,b} & k_{B,b} & k_{G,b} \\ k_{H,u} & k_{N,u} & k_{B,u} & k_{G,u} \\ k_{H,h} & k_{N,h} & k_{B,h} & k_{G,h} \end{pmatrix} \begin{pmatrix} D_H \\ D_N \\ D_B \\ D_G \end{pmatrix} = \begin{pmatrix} A_s \\ A_b \\ A_u \\ A_h \end{pmatrix}$$

D_H, D_N, D_B, D_G : Doses for hydrogen, nitrogen, boron and gamma-ray components

A_s, A_b, A_u, A_h : Absorbances for standard, boric-acid-added, urea-added and heavy-water-based gel dosimeters

$k_{H,s} \cdots k_{G,h}$: Parameters of each gel dosimeter for each dose component

Figure captions: Figure 1 Matrix equation for the relationship between absorbance of each gel dosimeter and the dose of each dose-component.

Introduction

Regular quality assurance (QA) is generally performed to ensure quality and safety in radiotherapy. However, optimal method for measuring and evaluating three-dimensional (3D) dose distribution in the body has not been established for QA in boron neutron capture therapy (BNCT) [1]. We are focusing on gel dosimeters, especially micellar gel dosimeters containing leucocrystal violet (LCV) [2], which can estimate the 3D dose distribution for BNCT. The 3D spatial dose information retained in the dosimeters after the irradiation can be easily measured using optical CT system [3]. In addition, the gel dosimeters can be easily made sensitive to specific dose-components by changing their compositions [4]. In BNCT, the following four dose-components are expected to be discriminated and estimated, such as boron dose, hydrogen dose, nitrogen dose and gamma-ray dose. Our final goal is to establish a method that combines multiple types of gel dosimeters sensitive to specific dose-components for the dose-component discrimination estimation. In this study, four types of LCV micellar gel dosimeters were prepared, such as a standard type and three types specified for boron, nitrogen and hydrogen dose-components. Boric acid was added as a sensitizer to the dosimeter for boron dose-component. Urea was added to the dosimeter for nitrogen dose-component. The heavy water-based dosimeter without additives was prepared for the estimation of the hydrogen dose-component, in which the difference in neutron scattering characteristic between light water and heavy water was utilized. It is assumed that the relationship between the absorbance of each gel dosimeter after irradiation and the dose of each dose-component follows the matrix equation shown in Fig. 1. The characterization experiments for the respective dose-components have been performed to determine each parameter “k” in this matrix equation [5]. Some of the results of the characterization experiments obtained so far are reported.

Materials and Methods

The compositions of the LCV micellar gel dosimeters were investigated by simulation code PHITS [6]. The characterization experiments were mainly performed using Heavy Water Neutron Irradiation Facility of Kyoto University Reactor (KUR-HWNIF) [7] and Cobult-60 Gamma-ray Irradiation Facility in the Institute for Integrated Radiation and Nuclear Science, Kyoto University (KURNS). In the experiments at KUR-HWNIF, three irradiation modes, such as the standard mixed neutron irradiation mode, the standard epi-thermal neutron irradiation mode and the standard thermal neutron irradiation mode, were used. The absorbance of the gel dosimeters after the irradiation was measured at the peak wavelength of 600 nm using a spectrophotometer (V730-Spectrophotometer, Japan Spectroscope Co., Ltd.).

Results and Discussion

From the experiment results, the effectiveness of the neutron sensitizer, especially boric acid, was confirmed. It was also confirmed that the dose response of each gel dosimeter depended on the linear energy transfers (LETs) of the particles produced in each dosimeter. The data analysis for the experiments is currently underway to evaluate each parameter “k”.

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Keywords: QA, gel dosimeter, dose-component discrimination

S2P23

Feasibility of high-definition 3D Dosimetry and Quality Assurance for Boron-Neutron Capture Therapy Clinics

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Background
In Neutron Capture Therapy (NCT), the radiation quality spans an unusually wide spectrum compared to conventional radiotherapy. Two consequences of this fact are of interest in the work reported here. First, there is a need for high-definition 3D dosimetry and quality assurance, both of which should include a microdosimetry component. Second, relevant radiation interaction cross sections, hence also the dose and LET distributions, are sensitive to the elemental composition of the phantom which must therefore be precisely controlled to simulate various tissues of interest. Here we report preliminary data from a feasibility study of achieving these goals using laser CT (LCT) of light-scattering polymer gel dosimeters (PGD).
Methods
Polymer gel dosimeters are tissue-equivalent gels containing acrylic monomers that undergo free radical chain polymerization when initiated by free radical products of radiolysis of the solvent or the solutes. In one type of PGD, the polymer forms permanent clusters large enough to scatter visible light according to Mie-Debye theory. As their concentration is proportional to dose, they form a visible, permanent 3D image in the gel. In addition, angular dependence of scattered light carries information about the sizes of the clusters, which appear to correlate well with LET [1]. Therefore, 3D LET mapping is likely to be realized using this technique. In another type of PGD, the polymer forms low-molecular-weight color centers, whose concentration is proportional to dose. The radiochromic signal naturally decays at temperature-dependent rates, making the dosimeter reusable. This assures signal stability during LCT scan and a faster signal decay before the next use. In addition to LCT scanning and static light scattering measurements, UV/VIS spectrophotometry of irradiated gel samples carries additional information about concentrations of the clusters and color centers and the cluster sizes. Finally, optical microscopy also shows the clusters and their tracks in the gel [2], which can be used to validate models of optical response to mixed fields, including those present in BNCT. Feasibility irradiations of gel samples in 20 cm long, 8 mm inner diameter Pyrex glass NMR test tubes were conducted at the National Centre for Nuclear Research.
Results and Discussion
UV/VIS spectra of light-scattering gels, exposed at NCBJ to fields that include both gammas (~60Gy) and thermal neutrons (~3Gy), showed significantly greater absorbance and a shift to longer wavelengths in gels that were doped with 70 ppm of 10-B as compared with gels without the dopant. Optical microscopy of exposed boron-doped gels revealed the presence of larger, visibly inhomogeneous polymer clusters, with diameters on the order of 10 microns, whereas the gels without the dopant, exposed to identical beams, showed clusters of ~1 micron diameters, appearing more homogeneous inside. The increased UV/VIS absorbance as well as the shift of the spectra to longer wavelengths in exposed boron-doped gels supports our hypothesis that the polymer cluster sizes increase with LET. So does the optical microscopy. UV-Vis difference spectra between boron-added PGD and PGD without ^{10}B, both exposed to identical fluxes of thermal neutrons, can distinguish the dose component due to products of the $^{10}B(n,\alpha)^{7}Li$ reaction from the baseline of $N^{14}(n,p)^{14}C$ and $H(n,\gamma)D$ reactions, identical in both gel types. More experiments are planned to add static light scattering data from an in-house built device in order to enable modeling of these phenomena and to use such models in quantitative 3D mapping of physical dose and LET using LCT of PGDs.
Acknowledgments
This work is supported in part by 1) a grant from the Polish National Agency for Academic Exchange, “Polish Returns” Program; and 2) by Gdańsk University of Technology internal grants ARGENTUM and AURUM under the national “Excellence Initiative – Research University” program.

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S2P24

Microdosimetric computational study of the effect of neutron source distributions and cell geometry modeling on HER2+ breast cancer in BNCT

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BNCT is a biologically targeted high-LET radiotherapy based on the radiobiological effects induced by the products released in the boron neutron capture (BNC) nuclear reaction. The stochastic nature of the process dictates the energy deposition in the cell nucleus, the main biological target. The isotropic emmission of alpha particle an lithium nucleus along with the intersection of their path with cellular structures together with microscopic distribution of boron atoms, are involved in this stochastic process. The short range of the neutron capture reaction products determine a highly localized energy deposition and, consequently, nuclear reaction spatial distribution is a relevant factor in the energy deposition distribution. Given the ongoing project that asesses the application of BNCT with immunoliposomes for the treatment of HER2+ breast cancer in Argentina (Gadan et al., 2015), the aim of this work was to study the effects of different BNC reaction sources distributions and cell geometry modeling on the energy deposition in the cell nucleus.
In this study, it was assumed that both cell and nuclear membranes volumes are convex bodies with spheroidal shape (Kellerer, 1984) characterized by both diameter, d, and elongation, e, parameters. On previous work, Santa Cruz proved that the chord-length distribution of an sphere can be recovered from analyzing its multiple cross-sectional chord-length distributions. Based on this, the computational modeling of cellular structures was performed on the analysis of chord-length distributions of segmented cell and nuclei membranes from images of histological sections of a HER2+ breast cancer tumor acquired by optical microscopy. A computational code was developed in Matlab environment to determine the spheroidal geometric parameters that best fit the chord-length distribution histograms of nuclei and cell membrane structures. In order to compute cell nucleus energy deposition, a computational code based on a stochastic-analog type simulation was implemented in Matlab environment. Monte Carlo method was employed for the stochastic generation of BNC reaction point sources from where light ions are emmitted isotropically with their respective energy and range. Some assumptions were made in order to perform these calculations: point sources from which light ions are emmitted are homogeneously distributed within cell compartments; the ions directions are isotropically distributed and their path are described by straight lines given by the range determined for the energy involved (Kellerer, 1969); energy deposition is uniformly distributed in the entire cell nucleus volume. Furthermore, the same material composition was assumed for the different cell compartments. The energy deposition along light ions path in cell nucleus was computed using stopping power values derived from Stopping and Range of Ions in Matter (SRIM). Finally, microdosimetric quantities, such as the lineal energy, y, and the frequency mean specific energy, zF, were obtained.
Based on the above, the analysis considered three spheroidal cell models, two of the prolate spheroid type (e > 1) and one spherical model (e = 1), and two distributions of neutron capture reactions, intranuclear and cytoplasmic. From the obtained zF values, the average number of events required to reach a prescribed absorbed dose in the tumor was calculated, obtaining that the distribution of intranuclear neutron capture reactions is more efficient compared to the cytoplasmic distribution. In addition, the concentration of boron required to reach the prescribed dose in the tumor was calculated from the average number of reactions for the established irradiation conditions. The theoretical values of boron concentrations were found to be within the experimentally observed range values, which were determined with neutron autoradiography and UV-C sensitization in HER2+ breast cancer cells.

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Keywords: microdosimetry, cell geometry, breast cancer

S2P25

Study of ionization chamber orientation in photon and neutron beams

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Ionization chambers are used in conventional external beam radiotherapy and BNCT dosimetry. Ionization chamber dosimetry is important part of periodic quality assurance and integral part of BNCT commissioning process. They are used especially for beam profile and depth dose measurements which are usually performed in a water tank. For full range measurements the size of the water phantom must be sufficient. Compared to ionization chambers used in conventional photon beam radiotherapy, the ones used in BNCT are typically larger in size to compensate for lower ionization rate in epithermal neutron beam. In addition, neutron beams used in BNCT have fixed horizontal beam direction which poses its own challenges to dosimetry measurements. Because of these reasons it could be much preferred to align the ionization chamber rod in parallel with the beam central axis instead of the perpendicular orientation which is typically used in calibration. Parallel orientation would allow us to perform over 40 cm range of profile (horizontal and vertical) and over 20 cm range of depth dose measurements with a single setup. However, because the parallel orientation differs from the reference orientation (perpendicular) the effects of the change must be known.
In this work we have investigated the effects and uncertainties of using the parallel orientation in comparison with the reference orientation [1]. The measurements were performed with Exradin T2 and M2 ion chambers in both 6X photon beam and epithermal neutron beam. The differences between the two orientations were determined by comparing the depth dose curves. The measurements made in both orientations were almost in agreement with each other with both ionization chambers and with both radiation sources. The curves measured in parallel orientation were within 2 % of the reference orientation and we would suggest using this additional uncertainty when using the parallel orientation instead of the reference. To further quantify the effects, we found two correction parameters by fitting, a correction factor k which adjusted the amplitude of the reading and a shift Δ which adjusted the effective point position of the ionization chamber in depth direction. We were able to convert data between the parallel and reference orientation with these two simple correction parameters. All correction factor results were within 0.985 – 1.015 and all shift results were smaller or the same order of magnitude compared to the positioning accuracy, (0.05 – 0.5) mm. This study confirms that ionization chambers may be used in parallel orientation with a good precision in photon and neutron beams.

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Keywords: dosimetry, ionization chamber, quality assurance

S2P26

Development of a Monte Carlo Simulation Framework for Advancing Dynamic PET Resolution in Boron Neutron Capture Therapy

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Boron Neutron Capture Therapy (BNCT) relies on the precise delivery of boron-10 to tumors while minimizing accumulation in blood and healthy tissues. The biodistribution of boron carriers over time is critical for determining the optimal time window for neutron irradiation. To achieve optimal therapeutic outcomes, irradiation should coincide with the period of the highest tumor-to-normal (T/N) ratio. Positron Emission Tomography (PET) emerges as a promising method for monitoring boron uptake in a time-resolved fashion by incorporating a positron emitter into the boron carrier. Dynamic PET imaging of boron carrier uptake in the tumor relative to surrounding normal tissues can predict BNCT effectiveness and aid in personalized treatment planning and patient selection. However, contemporary PET imaging faces a significant constraint due to its limited spatial resolution. The quantification of radioactivity by PET is contingent upon the volume of the target tissue, resulting in underestimation when the volume is generally less than 1 ml. Additionally, PET detectability is affected by cancer cell density. In cases of brain tumors with low cell density, identifying residual cancer cells can be challenging.
Understanding boron concentration at the macroscopic level (organs and tissues) is crucial for calculating absorbed doses in tumors and healthy tissues in BNCT. On the other hand, measurements at the microscopic level (cellular and subcellular) are crucial in BNCT for comprehensively understanding the biological effectiveness of various boron carriers. Tumor tissue comprises diverse cell components, such as cancer cells, stroma cells, immune cells, inflammatory cells, and blood vessels. In BNCT, the homogeneity of boron uptake and the concentration of boron-10 in each cancer cell directly influence therapeutic effectiveness. The short travel range of alpha and lithium-7 particles generated during the boron neutron capture reaction underscores the impact of the specific location of boron carriers within cell internal structures on BNCT's therapeutic efficacy. Microscopic measurements of boron concentration serve as the foundation for micro-dosimetry calculations. However, contemporary dynamic PET technologies are unable to attain the requisite high spatial resolution (<100 micrometres) for these microscopic evaluations. The positron's travel range before annihilation, e.g. approximately 0.54 mm for fluorine-18, also contributes to spatial resolution limitations. Insufficient PET resolution hinders the localization of tumors and the detailed assessment of boron distribution, impacting treatment planning, execution, and response assessment. The challenges related to spatial resolution are even more severe for PET imaging in real-time during BNCT treatment.
This study proposes a Monte Carlo simulation framework to develop methods and algorithms aimed at enhancing PET resolution, reducing noise, and optimizing image reconstruction in diverse BNCT scenarios. The objective is to address limitations and improve the effectiveness of dynamic PET applied in BNCT to achieve increasingly stringent goals.

Keywords: BNCT, PET, Monte Carlo simulation

S2P27

Feasibility study of the application of boron neutron capture therapy to Malignant Pleural Mesothelioma

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Boron neutron capture therapy (BNCT) is an experimental form of neutron therapy that allows selective delivery of radiation dose at the cellular level. This project intends to carry out a feasibility study on the treatment of malignant pleural mesothelioma (MPM), a cancer located in the pulmonary pleura, prospecting an innovative use of BNCT [1]. For this cancer, there is active research for finding boron compounds that target the tumor cells and which allows imaging [2]. Our study is aimed to demonstrate that with an accelerator-based BNCT (AB-BNCT) it is feasible to treat MPM in an advance stage. This is carried out using the Monte Carlo N-Particle Code (MCNP v6.2), which allows the simulation of neutron transport in different tissues with high accuracy. The feasibility study has been carried out using an adult woman voxelized phantom from the ICRP 110 [3]. The location of the tumor has been defined based on bad prognosis case reports present in the literature, with full coverage of the pleura on the left lung [4]. This choice produces an increased heart dose, therefore providing a worse case scenario. The upper limbs were removed from the model in order to have a better and more realistic access to the thoracic cavity. The neutron beam used for the feasibility study is modeled from the accelerator-based NeMeSis project at University of Granada, profiting from a very low fast neutron contamination given by the kinematically suppressed high energy neutrons from the 7Li(p,n) reaction at 2.1 MeV [5]. The source has been adapted using a large collimator of 24 cm diameter in aperture, in order to cover the pulmonary area in a better manner in a treatment of single fraction. One and two field treatments in a single session were considered for the optimization of the treatment plan, where the procedure included variation in both the positioning and orientation of the beam and the relative amount of irradiation time from each field. An uptake of 24 ppm of 10B in healthy tissues and 84 ppm in the tumor was assumed, following Suzuki et al [1]. The total irradiation time was determined from recommendations to the total dose surrounding organs at risk (e.g. heart, liver, pancreas) used in other forms of radiotherapy (attempting to use those with most similarities, as the few fraction stereotactic radio surgery (SRS) or stereotactic body radiation therapy (SBRT)). A set of Figures of Merit were defined in order to determine the best treatment plan from the optimization. Dose-Volume Histograms have been computed to assess the feasibility of using BNCT for mesothelioma. Results suggest that it is feasible to treat MPM in advanced stage with AB-BNCT.

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Keywords: malignant pleural mesothelioma,feasibility study,MCNP simulation,treatment

S2P28

Comparing the measured and simulated depth dose data in irradiation study with paraffin wax bolus in BNCT

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Purpose or Objective
Accelerator-based boron neutron capture therapy (BNCT) is based on epithermal neutrons that are thermalized in tissue and captured by ^{10}B nuclei that is accumulated in tumour cells. Capture reaction causes high radiation dose in target area compared to the surrounding tissue. However, in the superficially located tumours the dose may remain low. To increase the surface dose the use of a bolus is a standard method in radiation therapy. The aim of this study was to investigate the effect of a paraffine wax bolus to the depth dose distribution and to evaluate the equivalence between the measured and the simulated values calculated with GEANT4- based Monte Carlo simulation interfaced through the RayStation treatment planning system. Study was done by comparing the results of the measured and calculated number of activated target atoms in ^{55}Mn (n,γ)- and the ^{197}Au (n,γ)- foils in a water phantom with different bolus thicknesses. Paraffin wax and hydrogel boluses have previously been investigated at the BNCT facility located in the research reactor (FiR 1) in Helsinki, Finland with good outcome [1]. 3D-printed hydrogel bolus studies in Japan with A-BNCT have also been promising [2]. This study is part of the implementation of the new A-BNCT facility and its new treatment planning system in Helsinki, Finland [3]. Materials and Methods We investigated paraffin wax as a bolus material in a new accelerator-based treatment system in Helsinki University Hospital. Measurements were carried out with a large water phantom in three different cases: without a bolus and with 5 mm and 10 mm thick boluses. Depth dose data from different ^{55}Mn - and ^{197}Au- foil- geometries allowed to estimate how the depth dose curves shift as a function of bolus thickness. Simulations were done using RayStation treatment planning system with voxel-based calculation. Results and conclusion From the simulated and measured values, it was seen that the dose maximum shifted toward the skin surface when comparing the depth dose curves with bolus to the case without a bolus. The shift correlated to the thickness of the bolus. Furthermore, it was shown that simulated results from Raystation- treatment planning software were compatible with the measured ones.

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Keywords: Accelerator-based BNCT, dosimetry, bolus

S2P29

Boron Neutron Capture Enhancement Study for Radiotherapy with Fast Fission Neutrons

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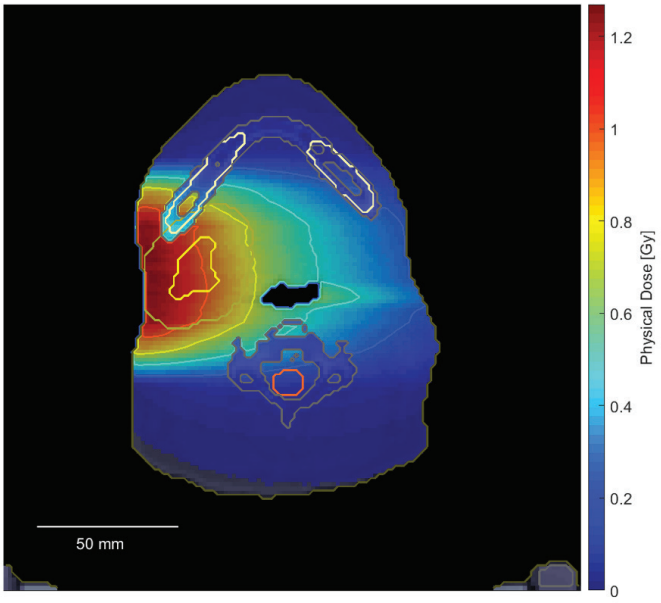

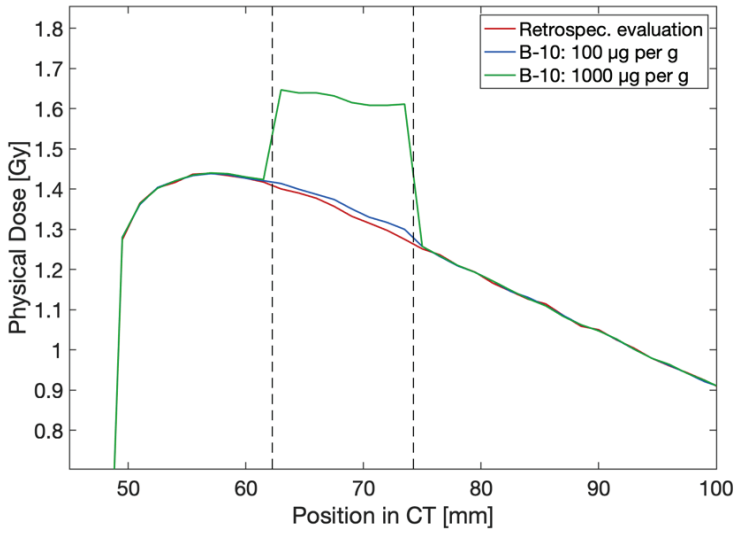

Figure captions:
Fig 1: Neutron dose deposition overlaid on planning CT calculated with MCNP.
Fig 2: Boron neutron capture enhancement for different B-10 concentrations

At the research reactor FRM II run by the Technical University of Munich, the medical applications instrument MEDAPP provides fission neutrons with a mean energy of 1.9(1) MeV for reactor-based fast neutron therapy (FNT) (Wagner et al. 2008). While MEDAPP is currently undergoing a general upgrade program, 126 patients mainly with superficial treatment indication were treated in the past (Specht et al. 2015).
With boron neutron capture therapy (BNCT) experiencing a revival over the last years, the development of new boron delivery agents allowing higher boron concentrations in tumor tissues becomes more likely. While BNCT is performed with neutrons initially in the thermal and epithermal energy range, fast fission neutrons are also thermalized in the patient mainly by scattering at hydrogen atoms producing secondary recoil protons. Depending on the fraction of thermalized neutrons in the vicinity of the tumor, a dose enhancement by boron capture might be beneficial for the treatment outcome. In an ongoing investigation, we investigate the BNC enhancement for typical FNT treatment scenarios at MEDAPP.
The dose deposition of the fast neutron treatment field is simulated with the general-purpose Monte Carlo code MCNP 6.2 (Werner 2017). A voxelized patient model is derived from treatment planning CT scans following a Hounsfield unit-based tissue segmentation in air, lung, soft tissue, and bone (cf. Schneider et al. (2000) & DeMarco et al. (1998)). For a patient with a salivary gland tumor treated at MEDAPP, four Monte Carlos calculations were performed: one retrospective calculation without boron in the tumor and three additional calculations with 20 µg, 100 µg, and 1000 µg B-10 per gram tumor tissue. The result of the retrospective Monte Carlo calculation without B-10 is shown in figure 1. A boron concentration of 20 µg/g is typically required for BNCT with thermal or epithermal neutrons (Barth at al. (2018) & Chandra et al. (2014)).
For the MEDAPP FNT treatment field, no enhancement of the dose deposition was found for a B-10 concentration of 20 µg per gram tissue. The enhanced dose depositions for the two higher B-10 concentrations are shown in figure 2 with reference to the retrospective dose calculation. While the high B-10 concentrations necessary to significantly enhance dose delivery in the tumor region are to our best knowledge currently not available in the clinic, the shown enhancement motivates further investigations with more generic calculation geometries and tuned fission neutron spectra.
In conclusion, the potential progress in the development of B-10 delivery agents motivates a broader feasibility study of BNC enhanced FNT at MEDAPP. Also, the expected increase in the biological effects in the tumor cells due to the short-ranged secondary ions released in the neutron capture reactions could be of benefit.

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Keywords: BNCT, FNT, Fission Neutrons

S2P30

Preliminary study for 3D dose distribution evaluation in neutron capture therapy using a PVA-GTA-I radiochromic gel dosimeter

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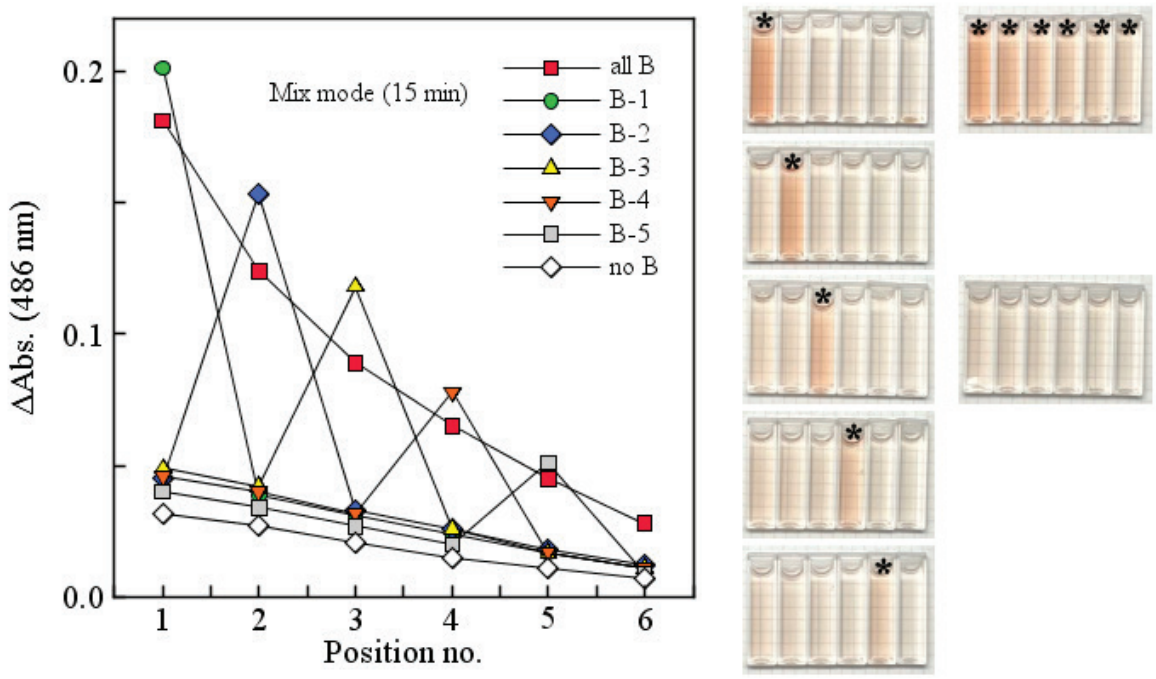

Figure captions: Figure 1 The change of absorbances in depth (corresponding to relative depth dose distribution) in mixed mode, and the irradiated gel dosimeters. The asterisks (*) indicate the samples with boron.

Introduction

Three-dimensional (3D) gel dosimeters have been developed for the 3D dose measurement of the complex conformal dose distributions in radiation therapy [1]. These devices are composed of radio-sensitive substances and an aqueous gel matrix to preserve spatial information about the absorbed dose. The 3D absorbed dose distribution is deduced from the distribution of the reaction products measured by 3D imaging modalities such as MRI and Optical CT. Gel dosimeters are regarded as tissue-equivalent to neutron radiation because their main component is water (>90%). In previous studies, polymer gel dosimeters that utilize radiation-induced polymerization reactions and Fricke gel dosimeters that utilize oxidation of ferrous ions have been applied to neutron beams [2-7]. On the other hand, in recent years, we have developed a PVA-GTA-I radiochromic gel dosimeter that utilizes red color development due to the complex formation of polyvinyl alcohol and iodide [8, 9]. This dosimeter exhibits excellent properties compared to conventional gel dosimeters, including high radiation sensitivity, dose rate independence, and thermal, temporal, and spatial stability. In our previous report, we applied this dosimeter to 2D dose distribution measurement for neutron beams and obtained results suggesting its usefulness [10]. In this work, as a preliminary experiment for evaluating the 3D dose distribution using optical CT, we evaluated the depth dose distribution in response to neutron beams from a nuclear reactor by combining small gel dosimeters with different compositions into blocks.

Materials and Methods

In this work, samples containing no $B(OH)_3$ (Standard) and containing 50 mM of $B(OH)_3$ with a natural ratio of ^{10}B (20%) were prepared. The resulting gels were subdivided by pouring into PMMA cuvettes (4 mL, 1 cm path length). The neutron irradiations were performed using Heavy Water Neutron Irradiation Facility (HWNIF) of Kyoto University Research Reactor (KUR, power of 1 MW) [11]. As shown in Figure 1, each set of the six samples was aligned vertically along the beam axis and irradiated from its side in the air at room temperature. Samples containing boron were placed at different depths along the beam axis, respectively. The three different modes (Mode-1: thermal neutron-rich, Mode-2: epithermal and fast neutron-rich, and Mode-3: the mixed modes) of neutron beams were applied to each sample set [12]. Absorption spectra of the samples were measured one day after irradiation using a UV-Vis spectrophotometer over the wavelength region of 350–800 nm. Absorbance was calibrated using a reference cuvette filled with distilled water. The change in absorbance (ΔAbs.) was obtained by subtracting the absorbance value of the non-irradiated sample from that of the irradiated samples. Each dose-response was evaluated using the change in absorbance at the absorption peak (486 nm).

Results and Discussion
Figure 1 shows the result in mixed mode as an example. The beam was delivered from the left side of the pictures. In the pictures, asterisks (*) indicate gel dosimeters containing boron. In the result, the color development attenuates from the surface (left) to the deeper parts (right) in all sets and the coloring becomes locally deeper in samples containing boron. Therefore, it is shown that the PVA-GTA-I gel dosimeter is effective for depth dose measurement and can measure sensitization due to boron against neutron irradiation. Similar results were confirmed in other modes. The results demonstrate the potential of the PVA-GTA-I gel dosimeter for future three-dimensional dosimetry using optical CT. The comparison with Monte-Carlo simulations will be also reported at this conference.

Acknowledgment
This work is supported by JSPS KAKENHI (Grant Numbers JP 20K08039).

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Keywords: gel dosimeter, BNCT, PVA-GTA-I, boron-10,

S2P31

Development of a compact neutron spectrometer for BNCT based on multi-element activation analysis

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In recent years, the introduction of accelerator-based BNCT facilities has led to a significant increase in interest from the medical and scientific communities. Monitoring and characterization of neutron beams and intercomparison of different facilities are becoming mandatory as specified by the IAEA [1]. This stimulates the development of dedicated dosimetry and spectrometry techniques. This work aims to present a novel compact spectrometer, based on the activation of a multi element geometry; the project has been funded by INFN. The detector is charachterized by an isotropic response and it is highly sensitive in the energy interval ranging from thermal to 100 keV, covering the whole epithermal energy range. This contribution will first focus on the extensive simulations work that have been performed to optimize the geometry of the detector, its materials composition, and its response. Thus, the main experimental results that have been obtained will be presented. In particular, the irradiation and activation measurements on a first prototype have been performed at the electron Linac facility installed at the university of Turin. In this facility, a well-known epithermal neutron field can be produced. The materials activation was measured using a HPGe and a LaBr(Ce) detectors, opportunely calibrated for the spectrometer geometry. A careful analysis of the activation gamma spectra has been performed to correctly estimate the statistic and systematic uncertainties. It should be noted that, using the LaBr(Ce) detector, the measurement system is evene more compact and transportable, making it possible in-situ measurements. The Turin epithermal neutron spectrum was then obtained using an unfolding code and a comparison with a standard Bonner Sphere Spectrometer (BSS) measure was performed. The agreement between the two measurements is within the 10%, providing a proof of the new spectrometer working capability. More details will be provided in the presentation. A compact multi-material spectrometer represents a novelty for the BNCT applications, with the aim to contribute to the beam quality assurance.

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Keywords: BNCT, spectrometer, compact, activation, gamma-analysis

S2P32

Potential of boron neutron capture therapy (BNCT) for myxofibrosarcoma

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Introduction:
Myxofibrosarcoma (MFS) is frequently observed in elderly patients, mainly in the subcutaneous tissues of the extremities. Although the first choice of treatment is wide surgical resection, amputation is occasionally requisite. MFS leads to severely curtailing activity of daily life, especially in the elderly. Also, the five-year survival rate being only 60%, we delved into the feasibility of applying BNCT to MFS patients, based on the newly established MFS cell line obtained from an MFS patient who had undergone amputation.
Materials and Methods:
A 66-year-old woman with recurrent MFS underwent upper left limb amputation, and a primary cell culture was generated from the tumor tissue. Additionally, an MFS-bearing animal model was created by transplanting the newly established MFS culture cells subcutaneously into the femoral region of nude mice. After the tumor had grown to almost 5 mm in diameter, BPA-Fr (24 mg ^{10}B/kg) was intravenously administered through the femoral vein of the MFS-bearing animal model under anesthesia. At a predetermined time thereafter, the MFS-bearing animal model was sacrificed, and blood and tissue samples were collected immediately for measuring the concentration of boron (^{10}B) by ICP-AES, and the tumor-to-blood (T/B) ratio of ^{10}B was calculated. In BNCT trials the MFS-bearing animals were divided into four groups (n=5). In groups A (BNCT group) and C (BPA control group), BPA-Fr (24 mg ^{10}B/kg) was administered through the femoral vein to the MFS-bearing animal model under anesthesia. Group D (cold control group) received neither boron nor irradiation. One hour after BPA-Fr dosing, thermal groups A and B (hot control group) were irradiated with thermal neutrons at Kyoto University Institute for Integrated Radiation and Nuclear Science (KURNS). The volume of the ellipsoid tumor mass in all groups was calculated. Two weeks after the irradiation, tumors in all groups were resected under anesthesia, and subjected to pathological analysis to confirm the antitumor effect of BNCT on MFS.
Results: In the clinical case, magnetic resonance imaging revealed areas of solid component anterior to the upper left limb. Although, ^{18}F-BPA-PET showed the uptake of BPA by only the tumor, the T/B ratio of ^{10}B was only 1.8. Microscopic examination of the resected tumor showed the solid component comprised low density tumor cells in the mucus substrate, as revealed in the histopathological analysis of the MFS-bearing animal model. After intravenous administration of BPA-Fr to the MFS-bearing animal model, ^{10}B concentration in the tumor was more than 20 ppm up to 80 min after the administration. In blood, on the other hand, ^{10}B decreased dramatically at 30 min., and the T/B ratio of ^{10}B at 60 min was 2.2, almost similar to that in the clinical case. Consequently, the duration of neutron beam irradiation (5 MW) was set at 10 min duration between 60 to 70 min after BPA-Fr administration. The irradiation dose to the MFS-bearing animal model was 15.7 Gy-Eq for group A and 2.3 Gy-Eq for group B. In groups B, C and D, no siginificant antitumor effect was acheived. In contrast, tumor growth was inhibited in group A at two weeks after irradiation. Histopathological studies revealed that the tumors were selectively destroyed only in group A.
Conclusions:
As in the clinical case, the T/B ratio was low in the animal model that carried the same tumor cells as those in the clinical case, which is attributed to the low density of tumor cells as shown through histological examinations. Boron uptake into individual tumor cells may likely be high. Indeed, antitumor effects were observed after BNCT to the MFS-bearing animal model. Since BNCT is expected to have a therapeutic effect on MFS, further relevant studies are warranted.

Keywords: myxofibrosarcoma, cell line, animal model,

S2P33

Use of semiconductor-based thermal neutron detectors for quality assurance in NCT facilities

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Activation foils, paired ionization chambers and fission chambers have been successfully used in Neutron Capture Therapy (NCT) facilities to monitor the neutron field and to determine spatial distributions of thermal neutrons in phantoms for Quality Assurance purposes [IAEA, 2023]. During the last decade the LEMRAP laboratory of INFN Frascati developed a series of semiconductor-based thermal neutron sensors for generic neutron monitoring purposes. Particularly, expertise was acquired in the field of high fluence rate with Silicon carbide detectors coated with ^{6}LiF using a customized electronic data acquisition chain and LabView routines. ^{6}LiF coating protocol used on these neutron sensors was also developed in our laboratory and is proved to be reproducible. Notably, these detectors are highly radiation resistant, very compact [Bedogni, 2022] and, due to their industrial origin, their price is limited. With the purpose of extending the use of these sensors to NCT, a feasibility experiment was designed based on the neutron beam available in the ENEA Frascati Neutron Generator (FNG) [Pietropaolo, 2018]. A simplified PMMA phantom was designed, allowing to locate a Silicon carbide sensor in different positions suited to describe a depth and a lateral profiles. On these particular conditions, calibration coefficients were obtained. The same profiles were described using the traditional method of the gold activation foils. The experiment work was complemented by the use of Monte Carlo simulations with MCNP 6.2 so that, in particular, energy distributions of the neutron fluence can be approximately known in the specific location of the detectors. The Silicon Carbide sensors satisfactorily reproduced the spatial distributions given by the gold foils. Furthermore, the measurements took seconds of beam time to be statistically significant and the responses were available immediately. Further work will include a “workplace-type” experiment where these compact neutron sensors will be used in a real radiotherapy phantom under an operational NCT neutron beam.

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Keywords: thermal neutron detector,silicon carbide,BNCT,FNG,gold foils

S2P34

Comparison of dose distribution with and without reflecting heterogeneous boron drug distribution using 18F-BPA positron emission tomography in boron neutron capture therapy

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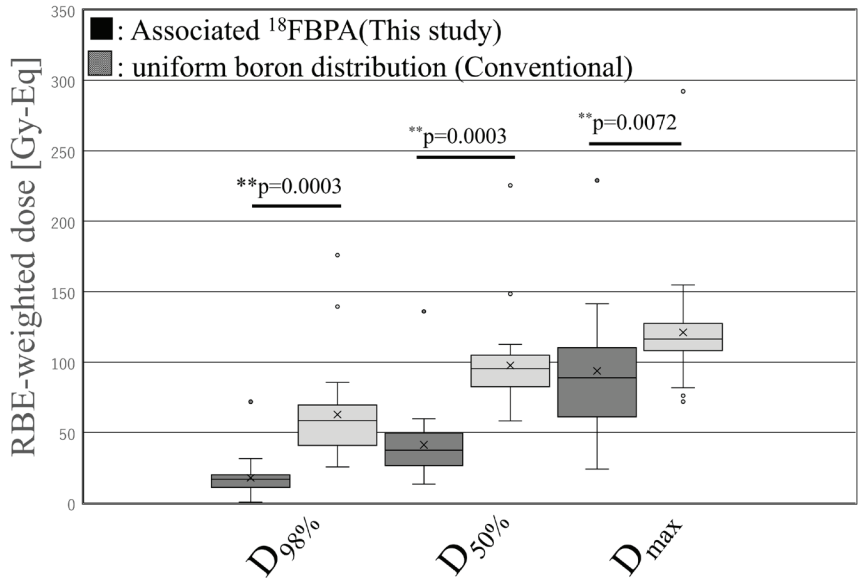

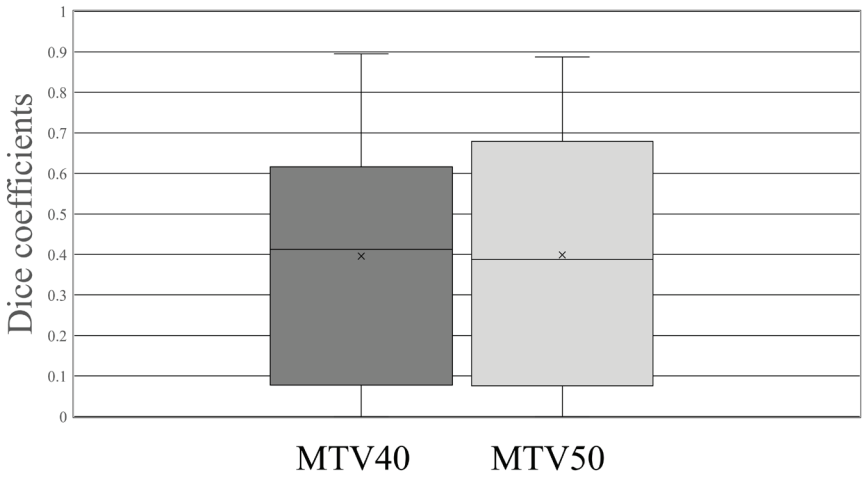

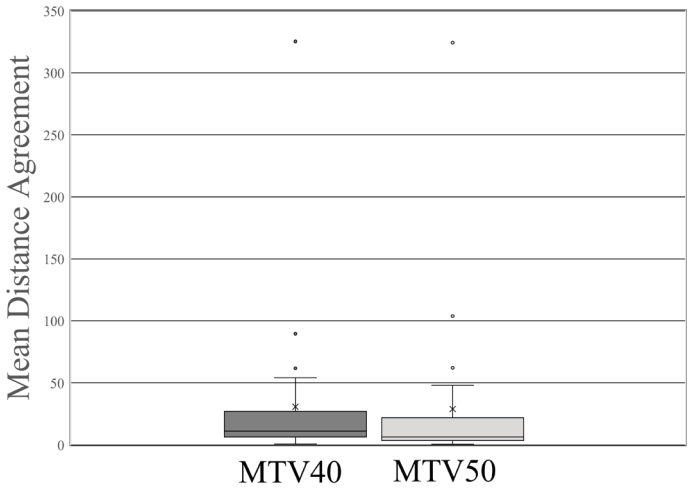

Figure captions:
Fig.1. Comparison of D98%, D50% and Dmax for GTV.
Fig.2. Dice coefficients for MTV40 and MTV50.
Fig.3. MDA for MTV40 and MTV50.

In boron neutron capture therapy (BNCT) dose evaluations, the boron drug is conventionally assumed to be uniformly distributed with specific values in each tissue. However, previous research suggested that the heterogeneous distributions and variations of boron concentration in each patient were reported using ^{18}F-fluoro-borono-phenylalanine(^{18}F-BPA) PET/CT and those related to the clinical outcome[1, 2]. This study investigated the necessity and the impact of implementing the heterogeneous boron distribution into the dose evaluations on tumors in BNCT.
Twenty-seven patients examined ^{18}F-BPA PET/CT at the National Cancer Center Hospital (NCCH), Tokyo, Japan, were applied in this study (Squamous cell carcinoma: 9, rhabdomyosarcoma: 5, adenoid cystic carcinoma: 2, melanoma: 2, glioma:2, angiosarcoma: 2, meningioma: 2, adenoma: 1, spindle cell carcinoma: 1, osteosarcoma: 1). Equivalent dose to gross tumor volume (GTV) was compared between the uniform boron distribution with specific values in each tissue (conventional method) and the heterogeneous boron distribution (novel method). In the novel method, the individual boron concentrations were determined based on the standard uptake value (SUV) on ^{18}F-BPA PET and the previously proposed equation, which was the estimation method of the boron concentration[3], and the dose evaluations were then performed in each patient. In the conventional method, the individual blood boron concentration was estimated from the SUV of the aorta and the proposed equation in each patient (i.e., the blood boron concentration was the same between the two methods). Tumor-to-blood boron concentration ratio was constant value of 3.5, and the dose evaluations were performed[4]. In both methods, the irradiation time was assumed as 60 min using the accelerator-based BNCT system at the NCCH (CICS-1, manufactured by the Cancer Intelligence Care Systems, Inc.) and the compound biological effectiveness of the tumor was assigned as 4.0 in this study[4]. The dose evaluations between the two methods were compared using the dosimetric parameters[5] (D98%, D50%, and Dmax). Furthermore, the metabolic tumor volumes (MTVs) were introduced to examine whether the clinical indicators from only ^{18}F-BPA PET which had been generally utilized (tumor-to-normal tissue ratio, etc.) were sufficient for BNCT. MTV50 and MTV40 were defined as the tumor regions of more than 50% and 40% of the maximum SUV in the GTV, respectively. In addition, the 50% and the 40% isodose-line in the tumor were introduced as the indicators of the dose evaluations considering the heterogeneous boron distribution. To compare those indicators between ^{18}F-BPA PET and heterogeneous dose evaluations, the dice coefficients and mean distance to agreement (MDA) were utilized.
The median blood boron concentration was 25.57 ppm (range: 19.36-78.39). Compared to the conventional method, the novel method showed the median of D98%, D50% and Dmax in GTV decreased 72.2%, 59.0%, and 20.1%, respectively (Fig.1). Comparing the regions between the MTVs and the isodose-lines, the median of dice coefficients between MTV40 and 40% isodose-line and MTV50 and 50% isodose-line were 0.42 (0.00-0.89) and 0.39 (0.00-0.88) (Fig.2), and median of MDA for those were 11.14 (0.64-325.36) and 6.39 (0.57-324.35) , respectively (Fig.3). These results showed no coincidence of high dose region with the region of ^{18}F-BPA concentration.
BNCT dose evaluations have been conventionally performed, assuming the uniform boron distribution of specific values depending on each tissue. However, using ^{18}F-BPA PET, there were discrepancies in the dose distribution in GTV with and without considering the heterogeneous boron concentration. Furthermore, there were discrepancies in the distributions between the ^{18}F-BPA PET and the dose evaluations considering the heterogeneous boron distributions. Therefore, this study suggested that the impact of the dose evaluations reflecting the heterogeneous boron distribution might be considerable, and such dose evaluation methods should be also considered to develop more useful clinical indicators for BNCT.

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Keywords: FBPA. PET. dosimetric correlation

S2P35

Implementation of OSLD for quality control of gamma ray dose measurement of an accelerator-based neutron source

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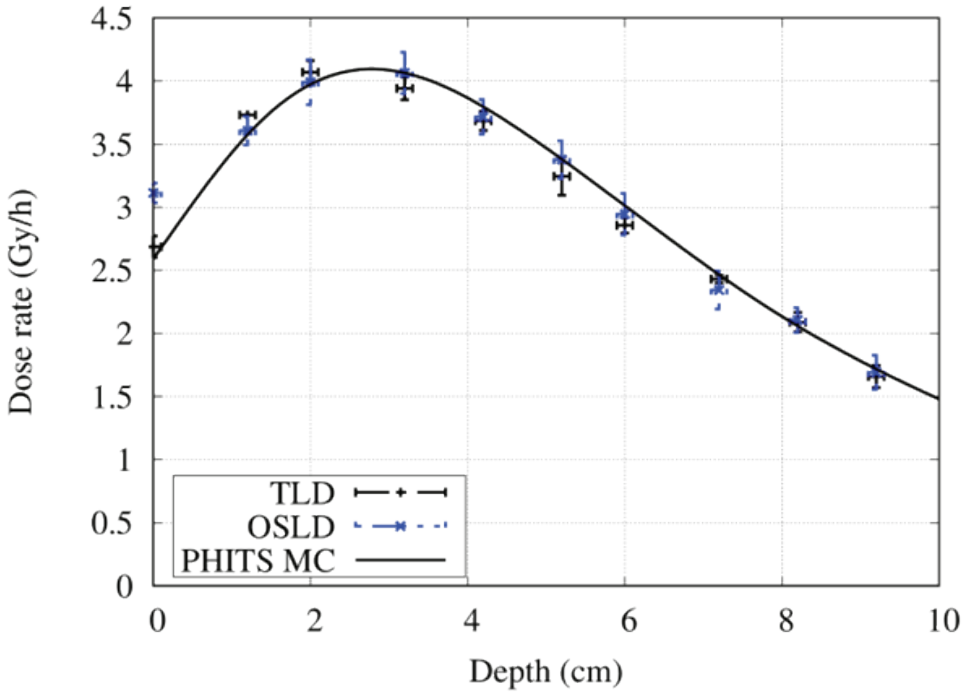

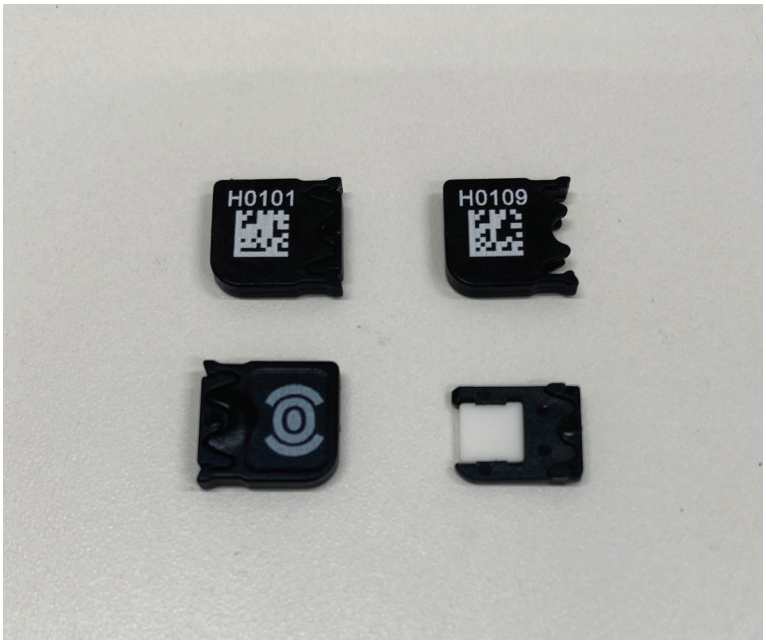

Figure captions:
1. Central axis depth dose curve measured with both OSLD and TLD inside a water phantom. The solid line indicates the PHITS Monte Carlo simulation result.
2. Image of the OSLD chip

A neutron source designed for boron neutron capture therapy is made up of a mixture of neutrons and gamma rays. These gamma rays are regarded as non-specific background dose that affects both the tumour and the surrounding healthy tissues, which cannot be ignored. An instrument for measuring the dose of gamma rays in a mixed neutron/gamma irradiation field is essential due to the growing number of BNCT accelerators. At the moment, gamma ray dose in a BNCT irradiation field is measured using BeO TLDs enclosed in quartz glass. However, this kind of TLD is no longer commercially available. To carry out the recommended ongoing quality assurance of gamma ray measurement for a clinical BNCT system, a replacement dosimetry system is needed. Recently, the use of OSLD detector systems have been investigated for gamma ray dose measurement in a mixed radiation environment. This study investigates the use of the myOSLD systems by RadPro International GmbH for routine quality control tests using a clinical BNCT system. The readout constancy, linearity, dose rate effect, and directional dependence of the OSLD were evaluated. The free-in-air and water phantom measurements were performed and compared with the TLD results and Monte Carlo simulation results. The readout constancy was found to be stable over a month-long period and similar to the TLD results. The OSLD readout signal was found to be linear with a high coefficient of determination (R^2 = 0.999) up to a proton charge of 3.6 C. There was no significant signal fading, dose rate nor directional dependency. The central axis depth dose and off-axis dose profile measurements agreed with both the TLD and Monte Carlo simulation results, within one standard deviation. A clinical BNCT accelerator system was used to characterise the myOSLD system. The OSLD achieved comparable, if not better, results than the dosimetry system currently used for routine quality control tests. The current TLD system could be replaced with the OSLD system to perform routine quality assurance of gamma ray dose measurement in a BNCT irradiation field.

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Keywords: Accelerator-BNCT, Gamma ray, OSLD, TLD

S2P36

Development of an attenuation correction probability model of list-mode MLEM for multi-angle Compton camera

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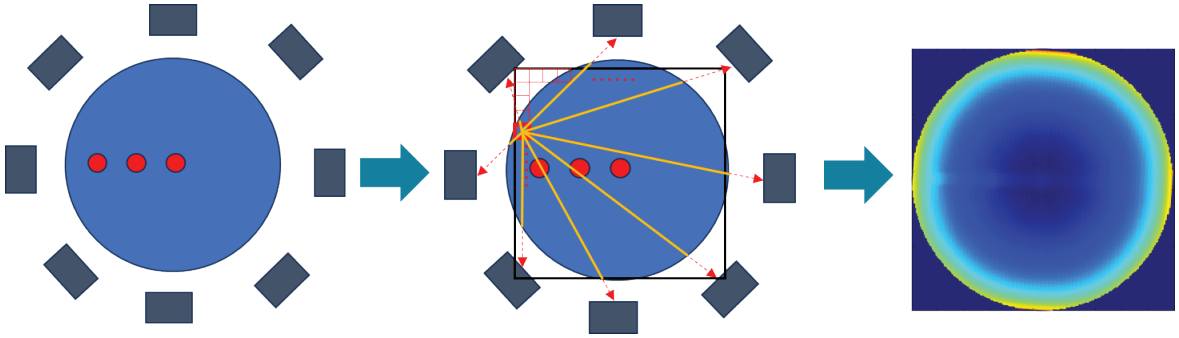

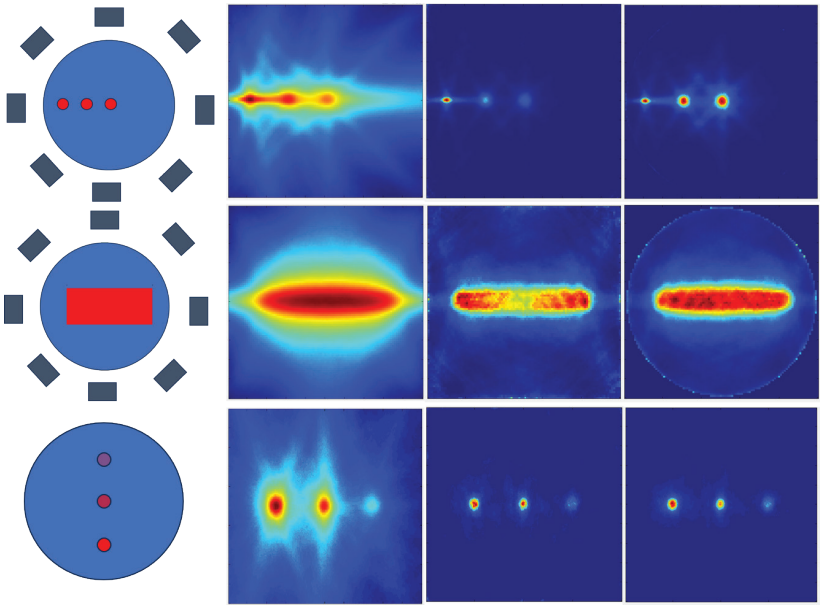

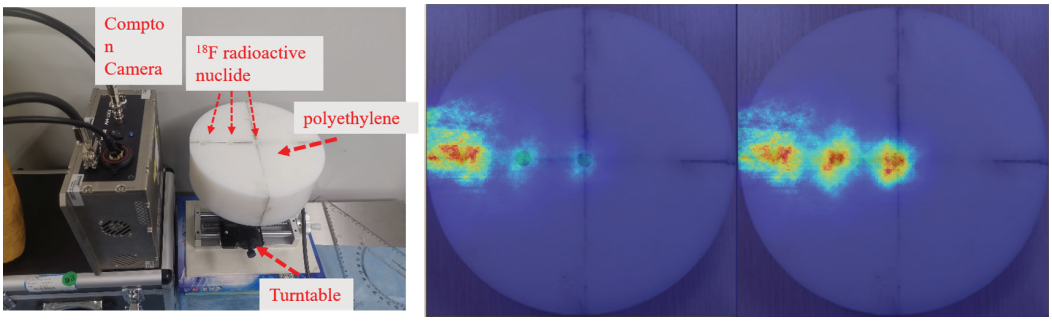

Figure captions:
Figure 1 The schematic diagram for the system matrix computation.
Figure 2 The reconstruction results simulated by Geant4.
Figure 3 The experimental platform and reconstruction results.

Backgrounds: The effectiveness of Boron Neutron Capture Therapy (BNCT) relies on the distribution of boron drug concentration within the patient's body during the treatment. To ensure an accurate assessment of BNCT effectiveness, real-time monitoring of boron drug concentration distribution within the patient's body is required throughout the treatment[1]. Compton cameras (CC) have garnered attention in nuclear medicine due to their broad energy detection range and high efficiency, offering promise for real-time monitoring of in vivo boron concentration in BNCT[2,3]. However, achieving real-time monitoring of BNCT boron concentration using Compton cameras still faces numerous challenges, with one key issue being the lack of suitable human tissue attenuation correction algorithms.

Materials and Method: An improved probabilistic model is proposed to correct the deviation in Compton event counts caused by tissue attenuation. This model incorporates the Beer-Lambert Law to compute the probability of tissue attenuation between imaging space pixels and detector positions, alongside Compton scattering cross-sections and geometry relationships[4]. This probability is integrated into the calculation of the system matrix within the list-mode maximum likelihood expectation maximization (MLEM) algorithm. To validate the model, utilizing Monte Carlo simulation software Geant4, an array of detectors at multiple angles (8 angles) and a cylindrical phantom model (simulating human body attenuation) were set up to investigate the attenuation correction effects on three-dimensional reconstruction of radioactive isotopes. Furthermore, to experimentally study the feasibility of this algorithm for tissue attenuation correction, a polyethylene phantom model was created, injecting ^{18}F radioactive isotopes at various depths, and the detection was performed using a 3D-CZT Compton camera (CZT crystal size 22 × 22 × 15 mm^3) rotated at 8 angles. The reconstruction effectiveness was evaluated through signal-to-noise ratio (SNR) assessment and Structural Similarity Index Measure (SSIM) and Root Mean Square Error (RMSE).

Results: Different algorithm reconstructions of simulated detected Compton events showed that SBP and MLEM reconstructions could only identify the source positions, with the reconstructed activity deviating from actual activity due to tissue attenuation. Using the probability model proposed in this study helped recover activity deviations caused by tissue attenuation, achieving a standard deviation of 0.194 for uniform planar sources. In the ^{18}F radioactive isotope experiment, the radioactive isotope activity reconstructed by this method was closest to the PET/CT reconstruction results. Comparing SBP, MLEM, and this algorithm, in scenarios of three-dimensional point, spherical, and planar source distributions, this method improved the structural similarity index and root mean square error by approximately 20%.

Conclusions: The CC attenuation correction algorithm proposed in this study can correct the influences caused by tissue attenuation. We validated the reconstruction efficacy of this algorithm through Monte Carlo simulations and experiments with radioactive nuclide, effectively compensating for human tissue attenuation. This advancement holds promise for achieving precise in-body real-time monitoring of BNCT boron concentration.

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Keywords: BNCT, ComptonCamera, AttenuationCorrection,PromptGammaRayImaging

S2P37

Evaluation of the expected annual therapist dose at a high-throughput BNCT Center

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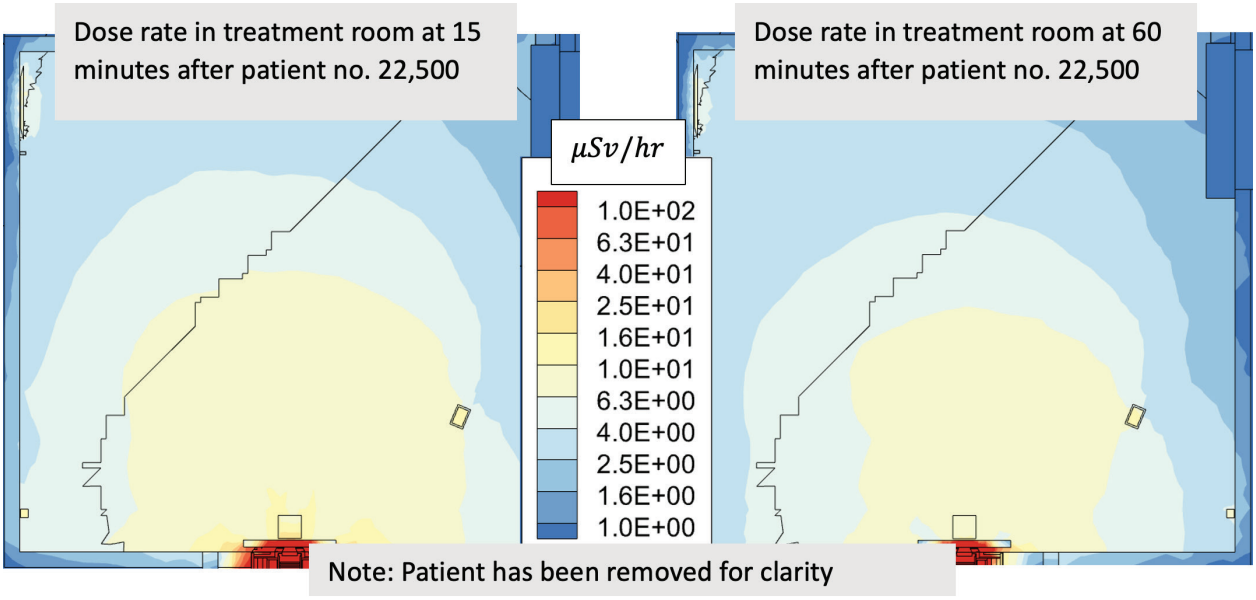

Figure captions: Expected dose rates from treatment room activation 15 minutes and 60 minutes, respectively following the treatment of the last patient (15 year workload)

A unique aspect of boron neutron capture therapy (BNCT) that differs from other radiotherapy modalities is the increased emission of secondary photons from decay of radioactive components due to neutron activation. An accurate accounting of neutron activation and resulting radiation doses in the treatment rooms, mazes, accelerator and high energy beam line rooms is necessary to assess the safety of members of the public, patients, service personnel and clinicians, especially therapists. A full radiological assessment has been performed to estimate the expected annual whole body dose for therapists at a high throughput BNCT facility using TAE Life Sciences' AlphabeamTM system. Conservative estimates assume a single therapist entering and exiting the treatment room for all clinical cases. Material choices for all Alphabeam components and items in the treatment room were determined to support a workload of 6 patients per treatment room per day, 5 days per week, 50 weeks per year, or 1500 patients per treatment room per year. The Alphabeam system lifetime was conservatively modeled as 15 years, i.e. the annual therapist dose is determined at the point of maximum overall activation and dose rate. Results estimate a therapist dose in this 15th year that is less than 4.5 mSv, which is well below regulatory limits, e.g. 50 mSv/year for the United States.(ref 1) Note that is more than one therapist is supporting each treatment room, or the patient throughput is less than 1500 per year, the annual therapist dose drops even more.
A rigorous two-step method was used to calculate the spatially dependent dose rates at multiple time steps in order to simulate the assumed clinical workflow. A key parameter of the model is minimum time betwen the end of neutron beam-on and therapist entry into the treatment room. This value, taken to be 5 minutes, may be lessened in restricted cases of patient need or emergent situations without excessively increase of the annual dose. The calculation utilizes 3D-CAD geometris and a neutron source term (full energy spectrum and angular dependence) for a 10 mA beam of 2.4 MeV protons incident on a thin lithium target. This 3D-CAD model, which includes all Alphabeam components, plus patient and auxiliary components in the treatment room, is converted into a tetrahedral mesh for use in the MCNP Monte Carlo code. The spatial saturation activity for each isotope is then converted to a time-dependent source of activation photons, assuming the workload described above. The second part of the rigorous two-step method uses the spatially resolved, energy dependent photon source term determined from the time-dependent adjustment of the saturation activity to calculate dose rates at various locations around the treatment room and adjacent facility. An example of these calculations is shown in Figure 1.

References: 1. NRC (2024, January) NRC Library, Subpart C – Occupational Dose Limits, United States Code of Federal Regulations.

Keywords: activation, dose limits, facility workload

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Relative biological effectiveness in an accelerator-based BNCT system coupled to a solid-state lithium target: two different approaches for neutron beams

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In recent years, the research and developments of accelerator-based boron neutron capture therapy (BNCT) systems have advanced, and the previous studies reported favorable clinical outcomes. The relative biological effectiveness (RBE) of neutrons generated from the BNCT systems, a crucial beam quality factor for clinical operation, were reported by Nakamura et al. and Hu et al. Nakamura et al. reported the RBE of an accelerator-based BNCT coupled to a solid-state lithium target. The other reported the RBE of an accelerator-based BNCT coupled to a solid-state beryllium target. The RBE is quantified by comparing the doses involving the cell surviving fraction (SF) of 10% (D10) between reference radiations (photons) and neutrons. However, doses of the neutron beam in the accelerator-based BNCT has not only neutron dose, but also contaminating γ-dose. Therefore, it is necessary to calculate the RBE of neutron by considering the γ-dose. Conventionally, the γ-dose was subtracted from the doses of the neutron beam to derive the neutron dose, and the RBE of neutrons was derived from the comparison of D10 between the reference radiations and the neutrons (RBE1). As proposed recently, an alternative method assumes that the contaminating gamma-rays and the neutrons in the neutron beam contribute to SF independently (RBE2). The contributions of the contaminating gamma-rays corrects the SF of the neutron beam using the SF curve of the reference radiations. Thus, this study evaluated the RBE of neutrons using those two different methods with an accelerator-based BNCT coupled to a solid-state lithium target, and those calculated values were then compared with the representative beam parameter in the accelerator-based BNCT to discuss the validity of RBE. Furthermore, the study also discussed whether the representative beam parameter in the system could be evaluated using those comparison. The experiments were performed at the National Cancer Center Hospital (NCCH), Tokyo, Japan, using the accelerator-based BNCT manufactured by Cancer Intelligence Care Systems, Inc. In addition, the experiments using the photon were performed using the medical linear accelerator (Clinac iX silhouettes, Varian Medical Systems, Palo Alto, CA, USA) at NCCH. Four cell lines (SAS, SCCVII, U87-MG, NB1RGB) were used to evaluate the SF. Cell SF curves of the neutrons and the photons were derived from the linear and the linear-quadratic (LQ) model, respectively, and the two models calculated D10. To acquire D10 in each cell line, the two models were applied to the SFs using the least-squares method. In the conventional method, the mean RBE1 value for four cell lines was 1.95, and the mean RBE2 value was 2.05 in the recently proposed method. The discrepancy of the two RBE values involved 4.9%, and it was comparable to the previous report from the other type of accelerator-based BNCT system. In addition, changes in RBE1 and RBE2 were evaluated when the ratio of contaminating gamma-rays to the neutron doses in the neutron beams, regarded as one of the representative beam parameters in the accelerator-based BNCT, varied. Apparently, the RBE2 value was not dependent on the different ratio. On the other hand, RBE1 values increased with increasing amounts of contaminating gamma-rays. When the ratio varied from -10% to 10%, the discrepancy between RBE1 and RBE2 ranged from 2.6% to 7.3%. Therefore, the discrepancy between RBE1 and RBE2 depends on the representative beam parameter in the accelerator-based BNCT. The two RBE values from the two methods might be less influenced when the specification of the system was designed for clinical use. Therefore, this study suggested that the comparison of the RBE values derived

from the two different methods could confirm not only the validity of RBE but also the representative beam parameter in the accelerator-based BNCT.

References:
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Keywords: accelerator-based BNCT ,RBE,contaminating gamma-rays,SF