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PLENARY

Plenary

PL133

Phase II clinical study of accelerator-based boron neutron capture therapy (BNCT) for patients with recurrent glioblastoma in Japan

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**The official name of Osaka Medical College has been changed to Osaka Medical and Pharmaceutical University as of April 1st, 2021.*

Background: Boron neutron capture therapy (BNCT) utilizes tumor-selective particle radiation. We aimed to assess the safety and efficacy of accelerator-based BNCT (AB-BNCT) [1] using a cyclotron-based neutron generator (BNCT 30) and 10B-boronophenylalanine (SPM-011) in patients with recurrent malignant gliomas (MGs), primarily glioblastoma (GB).

Methods: This multi-institutional, open-label, phase II clinical trial involved 27 recurrent cases of MG, including 24 GB cases, who were enrolled from February 2016 to June 2018. The study was conducted using the above-mentioned AB-BNCT system, with 500 mg/kg of SPM-011 (study code: JG002). The patients were bevacizumab-naïve and had recurrent MG after standard treatment. The primary endpoint was 1-year survival rate, and the secondary endpoints were overall survival (OS), and progression-free survival (PFS). The results were compared to those of a previous Japanese domestic bevacizumab trial for recurrent GB (JO22506).

Results: The 1-year survival rate and median OS of the recurrent GB cases in the current trial was 79.2% (95% CI: 57.0–90.8) and 18.9 months (95% CI: 12.9–NE), respectively, while those of JO22506 were 34.5% (90% CI: 20.0–49.0) and 10.5 months (95% CI: 8.2–12.4), respectively. The median PFS was 0.9 months (95% CI: 0.8–1.0) by RANO criteria. The most prominent adverse event was brain edema. Twenty-one of 27 cases were treated with bevacizumab following progressive disease.

Conclusions: The results of this BNCT clinical trial using a novel boron carrying drug, SPM-011, and a cyclotron-based epithermal neutron source (BNCT 30) showed a 1-year survival rate of 79.2% (95% CI: 57.0–90.8) and a mOS of 18.9 months for recurrent GB. Although direct comparison with other treatments is difficult, the results appeared to be favorable.

Keywords:
accelerator, boron neutron capture therapy, clinical trial, glioblastoma

Acknowledge:
The trial was a success with support from many people who could not be mentioned. And most importantly, the authors are very appreciative of all the patients and their supportive families for participating in this trial.

References:

[1] Tanaka H, Sakurai Y, Suzuki M, et al. Nucl. Instrum. Methods Phys Res B. 2009; 267:1970-1977

Towards clinical trial of iBNCT project.

Akira Matsumura[1], Hiroaki Kumada[1], Yinuo Li[1], Susumu Tanaka[1], Yoshitaka Matsumoto[1], Kei Nakai[1], Takeji Sakae[1] Koichi Hashimoto[2], Fujio Naito[3], Toshikazu Kurihara[3], Takashi Sugimura[3], Masaharu Sato[3], Yukihide Kamiya[3] , Hideyuki Sakurai[1]

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The iBNCT project has been started in 2012 as "Tsukuba International Strategy Zone Project 1" supported by Cabinet office of Japan, Ministry of Economics, Trade and Industry, Japan Agency for Medical Research and Development (AMED) and several other research funds.

The main researchers group were from University of Tsukuba, High Energy Accelerator Research Organization (KEK) and private sectors. The first prototype accelerator has been installed at Ibaraki Neutron Medical Research Center (iNMRC) at Tokai, supported by Ibaraki-prefecture.

The concept of the iBNCT project was to develop a compact accelerator suitable for hospital use with a special regards to low radioactivity of the machine and surrounding facility and produce neutron beam suitable for BNCT. Therefore, the proton energy was selected as 8 MeV which is below the threshold of activating the different metal material used for the accelerator. The peak neutron energy produced by 8 MeV proton is about 6.1 MeV so that the accelerator and the surrounding environment may keep low radioactivity after the treatment. So far, the radioactivity just after the accelerator operation is very low, which is about 40 μSv/hr at around the beam aperture. The neutron beam produced by 0.5 mm thick beryllium is mainly within the epithermal zone which is similar to JRR-4 epithermal beam mode but slightly higher epithermal components compared to JRR-4 reactor beam.

The details of accelerator performance will be presented by Dr. Kumada at "neutron sources" session at this conference, but briefly the epithermal neutron flux in the free-in-air condition is at the center of the aperture is approximately 8×10^8 (n/cm^2/s) with the average proton beam current of 2.1 mA and 5 mA beam current is being process in the development. With the current performance, we are now planning to perform phase I/II clinical trial for recurrent head & neck (H&N) cancers as a first step and started counseling with Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. The preliminary physical and biological experiments have been started at iNMRC Tokai and the performance seems to be ideal for clinical BNCT so far.

After clinical trials, we are planning to apply this equipment for approval as medical device and start the medical treatment at iNMRC Tokai or Proton Medical Research Center at University of Tsukuba Hospital. The treatment planning system (so called Tsukuba plan) and patient setting systems will be also installed in whole treatment system and it may be applied for malignant glioma and malignant meningioma (clinical trial is ongoing in Japan) after clinical trial using this equipment.

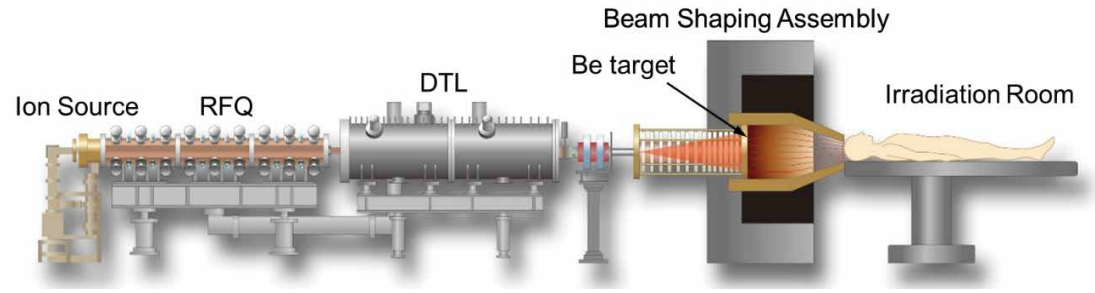

Fig. 1 Schematic image of iBNCT001

Status update of the accelerator-based boron neutron capture therapy facility at Helsinki University Hospital

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Boron Neutron Capture Therapy (BNCT) is a biologically targeted binary radiotherapy method developed to treat patients with certain malignant tumors. Helsinki University Hospital is going to start BNCT treatments in near future using a compact accelerator based neutron source, which can be installed in a hospital environment. The safety and efficacy of the L-BPA-F mediated BNCT, have previously been evaluated in the clinical protocols of head and neck carcinomas and malignant gliomas at the Finnish research reactor FiR 1[1].

Commissioning of the accelerator-based BNCT facility manufactured by Neutron Therapeutics Inc. started mid 2018. The 2.6 MV electrostatic proton accelerator is designed to operate at 30 mA, and the neutrons are produced by a rotating lithium target. The nuBeam treatment suite includes a CT image guided robotic patient positioning system, and a Monte Carlo based treatment planning software designed for BNCT. Radiation Safety Authority of Finland has measured the radiation levels during and after the beam operation and have approved the usage of the facility for commissioning.

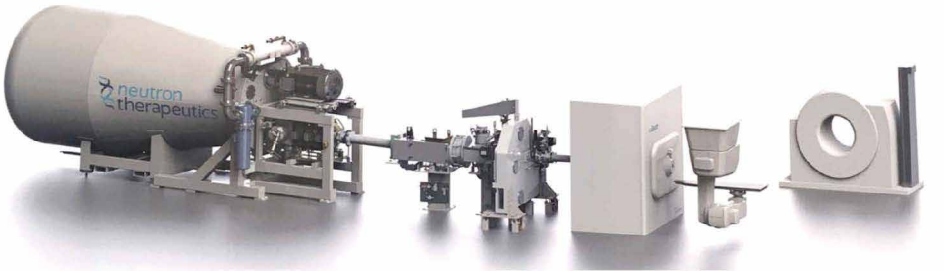

Figure 1. nuBeam compact accelerator based neutron source

Neutron beam characteristics in air, and profiles and depth dose curves in water and PMMA phantoms have been measured using neutron activation analysis with various materials, TE(TE) and Mg(Ar) ionization chambers, and results are consistent with design goals that also fulfill the recommendations of IAEA TECDOC-1223 [2]. Radiation dose rate in the treatment room is measured routinely after each beam operation, and the results confirm a low activation level with a fast decay, allowing the personnel to enter in the room shortly after the termination of the irradiation

After the commissioning of the neutron beam, patient positioning robot and the CT scanner and approval by the local authorities, the first clinical trial will be initiated on patients within operable recurrent head and neck cancer.

Keywords:
Accelerator, facility, commissioning

References:

[1] Kankaanranta et al. Int J Radiat Oncol Biol Phys. 2012.
[2] IAEA-TECDOC-1223. International Atomic Energy Agency, 2001.

BNCT@CNAO: a multidisciplinary research collaboration project

S. Rossi on behalf of BNCT@CNAO Collaboration

CNAO Foundation

CNAO Foundation will team with INFN, Polytechnic of Milan and University of Pavia (the BNCT@CNAO Project) to introduce, for the first time in Italy, a new particle accelerator for the production of neutron beams for Boron Neutron Capture Therapy. The accelerator is realized by the US company Tae Life Sciences and will be installed at CNAO, Pavia (Italy), in an area dedicated to clinical and medical research.

Pavia has already been a pioneer in this technique, thanks to the work carried out in the early 2000s by experts from the Policlinico San Matteo, the University of Pavia and the National Institute of Nuclear Physics (INFN). This wealth of experience will find new life in the project BNCT@CNAO. Two irradiation rooms will be built and served by a tandem proton accelerator: one devoted to research and the other reserved to patients treatment. Treatment rooms include fixed beam line, beam shaping assembly and a ceiling-mounted robotic couch for optimal patient positioning.

Due to its characteristics, BNCT requires multidisciplinary research, involving physicists and engineers for the design and implementation of the technology necessary for the production of neutron beams; chemists and biologists for the study and optimization of the bio-distribution of boron and the analysis of radiobiological effects; physicists and physicians for dosimetry, preparation of treatment plans and patient management. This ambitious project could be realized putting in place a strong and multidisciplinary collaboration, involving the main academic and research institutes that have always been cooperating with CNAO since the beginning. The BNCT@CNAO Project will be focusing on integrating and expanding the current knowledge in BNCT in order to achieve the best possible beam from an accelerator based neutron source, possibly together with a novel boron molecule carrier. The four institutions constitute the core group of the pre-clinical and clinical research effort, but they are since the beginning open to new world-wide collaborations aiming to power the efficacy of this treatment modality.

Radiobiological research, dosimetric models and treatment planning simulations, boron measurements and clinical dosimetry will be duly pursued in order to verify the higher ability to selectively destroy neoplastic cells, sparing healthy ones, provided that the carrier capacity of “recognizing” neoplastic cells is very enhanced. In parallel, patients selection criteria, eligible pathologies and treatment protocols will be investigated. Research perspectives include also the development of new drugs for the administration of Boron-10.

Keywords:

Boron Neutron Capture Therapy, multidisciplinary research, radiobiology, dosimetry, treatment planning simulations, boron bio-distribution

PL172

Neutron source VITA: from an idea to a clinic and fundamental knowledge

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A compact neutron source has been proposed and created at the Budker Institute of Nuclear Physics to obtain a neutron beam that largely meets the BNCT requirements. The source comprises an original design tandem accelerator (Vacuum Insulated Tandem Accelerator), a solid lithium target, and a beam shaping assembly. The accelerator is used to provide a dc proton/deuteron beam. The ion beam energy can be varied within a range of 0.6–2.3 MeV, keeping a high-energy stability of 0.1%. The beam current can also be varied in a wide range (from 1 pA to 10 mA) with a high current stability (0.4%). The unique capabilities of the facility allow: i) to generate an epithermal neutron flux with characteristics suitable for BNCT; ii) to generate thermal neutrons for determining the impurity content by the activation analysis, in particular, in ceramic samples developed for ITER; iii) to obtain a diagnostic neutron beam of an epithermal energy range without the presence of fast and thermal neutrons in it for boron imaging; iv) to generate a powerful flux of fast neutrons for radiation testing of optical fibers for CERN; v) to form a bright source of monochromatic γ-rays with an energy of 478 keV for measuring the ^{7}Li(p,p'γ)^{7}Li cross-section and the contribution of the fast neutron dose and the ^{14}N(n,p)^{14}C reaction dose to the absorbed dose during BNCT, vi) to generate 9.17 MeV γ-rays with the ^{13}C target for detecting explosives; vii) to study the energy and angular characteristics of the ^{11}B(p,α)αα reaction. The neutron source served as a prototype for the facility created for a clinic in Xiamen (China) and the facilities being created for the CNAO in Pavia (Italy) and the Oncology Center in Moscow (Russia). The report describes the features of the facility, the results of its application, and plans for future research.

Keywords:
charged particle accelerator, neutron target

The Importance of Animal Studies to Evaluate the Clinical Potential of Boron Delivery Agents for Neutron Capture Therapy (BNCT).

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Despite the passage of over 50 years since the introduction of the two clinically approved boron delivery agents, sodium borocaptate or BSH ($Na_2B_{12}H_{11}SH$) and boronophenylalanine (BPA), there still are no new boron delivery agents for clinical use. The simple question is why? Although there now is an extensive chemical literature on a wide variety of potential boron delivery agents for BNCT,[1] with the single exception of a carboranyl porphyrin, none has been evaluated in animals larger than mice or rats, because there have not been sufficiently promising biodistribution, toxicologic, and therapeutic data to warrant large animal or human studies. This lack of new and better boron delivery agents has greatly impeded the advancement of BNCT.

This presentation focuses on our studies with BSH, BPA,[2, 3] boronophorphyrins,[4] and boronated monoclonal antibodies (MoAbs) directed against the epidermal growth factor receptors, EGFR and $EGFR_{VIII}$.[5, 6] These studies have used the F98 rat glioma as a model for human high grade gliomas.[7] We first focused on optimizing the delivery of BPA and BSH either alone or in combination, using intracarotid (i.c.) injection of a hyperosmotic solution of mannitol[1] or Cereport (RMP-7), a bradykinin analog, to disrupt the blood-brain barrier (BBB-D).[3] These studies demonstrated that i.c. administration of mannitol or Cereport significantly increased tumor boron concentrations of both BPA and BSH and the mean survival times (MST) of tumor bearing rats compared to survival times of those receiving intravenous (i.v.) BPA (MST 95d vs 33d). However, this approach hasn't been used clinically because the procedure is too complicated to be employed in a non-hospital setting. Although current clinical practice calls for i.v. administration of BPA and BSH, this should be re-evaluated since experimental animal data have shown that i.c. administration can significantly increase tumor boron concentrations of both BPA and BSH.[2] Our studies of i.c. delivery of Cereport in combination with BPA resulted in a 3.6x increase in tumor boron concentrations in F98 glioma-bearing rats and a 2.4x increase in MST.[3] Drugs that can open the BBB comprise an important area of research and could lead to significant improvements in brain tumor uptake of BPA and BSH.

In regard to high molecular weight (HMW) boron delivery agents such as boronated MoAbs directed against EGFR or $EGFR_{VIII}$,[1] i.v. injection failed to deliver adequate amounts of ^{10}B. Therefore, we turned to direct intracerebral administration using convection enhanced delivery (CED) in combination with i.v. administration of BPA.[5, 6] This resulted in a 1.8x increase in MST. Direct administration of HMW agents to the tumor site may be essential to achieve therapeutically effective concentrations of ^{10}B in brain tumors. However, as our study with carboranyl porphyrins has shown,[4] caution is required in relying solely on tumor boron concentrations. In this study, the tumor ^{10}B concentration of a tetra (4-nido-corboranylphenyl) porphyrin (H_2TCP) following intracerebral administration by Alzet pumps over 24h was the highest that we ever had obtained (149.6 µg B/g tumor).[3] However, the MST of these rats was similar to that obtained by i.v. administration of BPA (35.0d vs. 39.8d). Microscopic examination of the rat brains revealed that the porphyrin had been taken up primarily by tumor infiltrating macrophages rather than tumor cells. Our studies clearly have demonstrated that different delivery approaches will be required for low vs. HMW delivery agents for both brain and extracranial tumors.[8]

Ending on a positive note, the current focus should be on improving dosing paradigms and delivery of BPA and BSH. One such approach is pulsed ultrasound, which could have an immediate clinical impact.[9]

Keywords:
BPA, BSH, MoAbs delivery, F98 glioma

References

[1] Barth RF, Mi P, Yang W. Boron delivery agents for neutron capture therapy of cancer. Cancer Commun (Lond) 2018; 38: 35.
[2] Barth RF, Yang W, Rotaru JH et al. Boron neutron capture therapy of brain tumors: enhanced survival following intracarotid injection of either sodium borocaptate or boronophenylalanine with or without blood-brain barrier disruption. Cancer Res 1997; 57: 1129-1136.
[3] Yang W, Barth RF, Bartus RT et al. Improved survival after boron neutron capture therapy of brain tumors by Cereport-mediated blood-brain barrier modulation to enhance delivery of boronophenylalanine. Neurosurgery 2000; 47: 189-197; discussion 197-188.
[4] Kawabata S, Yang W, Barth RF et al. Convection enhanced delivery of carboranylporphyrins for neutron capture therapy of brain tumors. J Neurooncol 2011; 103: 175-185.
[5] Wu G, Yang W, Barth RF et al. Molecular targeting and treatment of an epidermal growth factor receptor-positive glioma using boronated cetuximab. Clin Cancer Res 2007; 13: 1260-1268.
[6] Yang W, Wu G, Barth RF et al. Molecular targeting and treatment of composite EGFR and EGFRvIII-positive gliomas using boronated monoclonal antibodies. Clin Cancer Res 2008; 14: 883-891.
[7] Barth RF, Kaur B. Rat brain tumor models in experimental neuro-oncology: the C6, 9L, T9, RG2, F98, BT4C, RT-2 and CNS-1 gliomas. J Neurooncol 2009; 94: 299-312.
[8] Hiratsuka J, Kamitani N, Tanaka R et al. Boron neutron capture therapy for vulvar melanoma and genital extramammary Paget's disease with curative responses. Cancer Commun (Lond) 2018; 38: 38.
[9] Barth RF, Grecula JC. Boron neutron capture therapy at the crossroads - Where do we go from here? Appl Radiat Isot 2020; 160: 109029.

Quantification of target elements in individual cells by Single Cell ICP-MS for medical applications: New instrumental capabilities

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The possibility of quantification of elemental concentrations at the level of individual cells is allowing new insights and advances in medical applications and cancer research. In this presentation the principles of the SC-ICP-MS technique will be explained, applications examples will be reviewed for both ionic and nanoparticulate target element uptake. New instrumental capabilities will be discussed.

PL49

BNCT for recurrent and refractory high-grade meningioma (Reactor to Accelerator)

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Background: High-grade meningioma (HGM) is difficult to treat, and recurrent HGM after radiotherapy has an especially poor prognosis. We retrospectively analyzed the cases of 44 consecutive patients with recurrent and refractory HGM who were treated by reactor-based boron neutron capture therapy (BNCT).

Methods: In 2005–2019, we treated 44 recurrent and refractory HGMs by reactor-based BNCT. We analyzed the patients' tumor shrinkage, overall survival (OS) after initial diagnosis, OS after BNCT, progression-free survival (PFS) post-BNCT, and treatment failure patterns. Also we analyzed the relationship of total radiation dose for normal brain (pre-BNCT radiation dose and BNCT dose) and the incidence and severity of radiation damage.

Results: The median OS (mOS) after BNCT and mOS after initial diagnosis were 29.6 (95%CI: 16.1–40.4) and 98.4 (95%CI: 68.7–169.4) months, respectively. The median follow-up after BNCT was 26 (6.4–103) months. The grade 2 (20 cases) and 3 (24 cases) post-BNCT mOS values were 44.4 (95%CI: 27.4–not determined) and 21.55 (10.6–30.6) months, respectively (p=0.0009). Follow-up images were obtained from 36 cases at >3 months post-BNCT; 35 showed tumor shrinkage during the observation period. The post-BNCT median PFS (mPFS) of 36 cases was 13.7 (95%CI: 8.3–28.6) months. The post-BNCT mPFS values in patients with grade 2 and 3 disease were 24.3 (95%CI: 9.8–not determined) and 9.4 (6.3–14.4) months, respectively (p=0.0024). Local recurrence was observed in only 22.2% of cases. These results showed good local tumor control and prolonged survival for recurrent HGM cases. Figure 1 shows the representative case of recurrent and refractor case of WHO grade 3 meningioma treated by reactor–based BNCT. The total EQD2 of the preceding radiotherapy and BNCT for the normal brain adjacent to the lesions was compared between the patients with radiation necrosis grades 0+1 (treatment unnecessary) and radiation necrosis grades 2+3 (treatment necessary). The mean EQD2 ± SD values for the two groups were 77.2 ± 32.6 and 109.6 ± 30.5, respectively, and these values were significantly different by Wilcoxon rank sum test (p=0.0153).

Conclusions: Most of these cases had relatively large tumor volumes. The proportion of grade 3 patients was extremely high. Our patients thus seemed to have poor prognoses. Nevertheless, reactor-based BNCT exerted relatively good local control and favorable survival for recurrent and refractory HGMs. Based on these experiences using reactor-based BNCT, now we are performing randomized controlled trial of accelerator based BNCT for high-grade recurrent and refractory meningiomas.

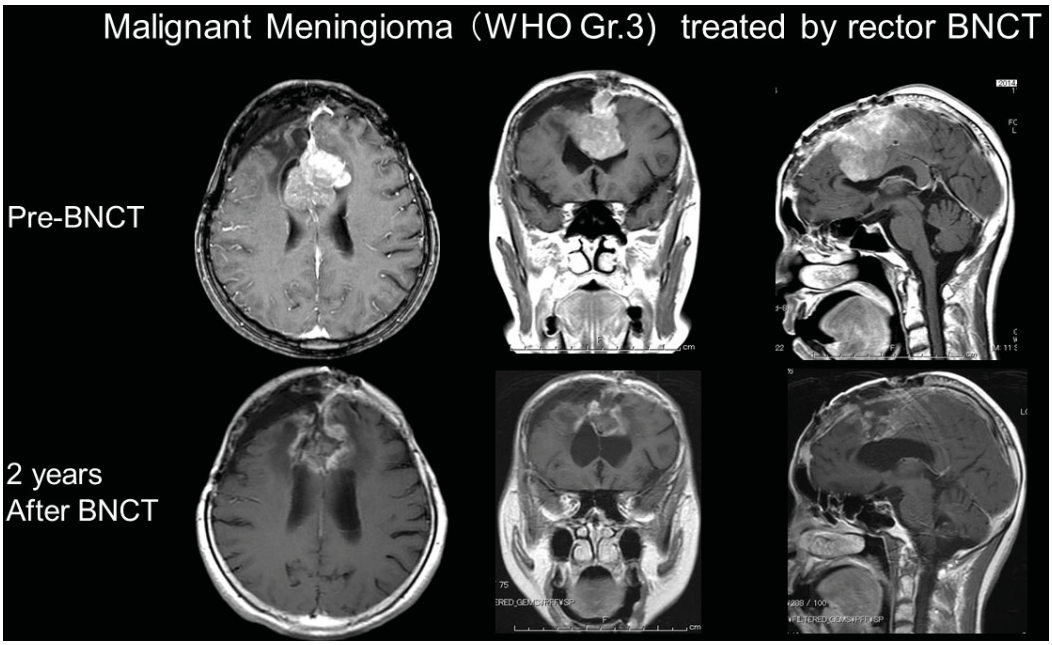
Malignant Meningioma（WHO Gr.3） treated by rector BNCT
Pre-BNCT
2 years
After BNCT

Figure 1

PL53

Towards the application of purely inorganic neutral and anionic icosahedral boron clusters in nanomedicin.

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Aromatic compounds that play important roles in biochemistry found numerous applications from drug delivery to nanotechnology or biological markers. We have reached important achievement demonstrating experimentally/theoretically that neutral and anionic carboranes, as well as anionic metallacarboranes, 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] and nanoparticles 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],[4] may result in significant clinical benefits for glioblastoma treatment. Parallel to their use as BNCT agents, boron clusters have been found to be very good scaffolds for diagnostic and therapeutic labelling,[5] opening the door to a wide range of biomedical applications. The interactions of metallabis(dicarbollides) with biomolecules (proteins,[6] ds-DNA[7] and glucose) as well as their translocation through bilayer membranes have been studied.

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

References:

[1] J. Poater, C. Viñas, I. Bennour, S. Escayola, M. Solà, F. Teixidor. "Too Persistent to Give Up: Aromaticity in Boron Clusters Survives Radical Structural Changes." J.Am.Chem.Soc., 2020, 142, 9396−9407.

[2] C. Viñas."The Uniqueness of Boron as a novel challenging element for drugs in pharmacology, medicine and for smart biomaterials". FutureMed.Chem., 2013, 5(6), 617-619; C. Viñas, R. Núñez, I. Bennour, F. Teixidor. "Periphery Decorated and Core Initiated Neutral and Polyanionic Borane large molecules: Forthcoming and Promising properties for medicinal applications". Curr.Med. Chem., 2019, 26(26), 4935-4951.

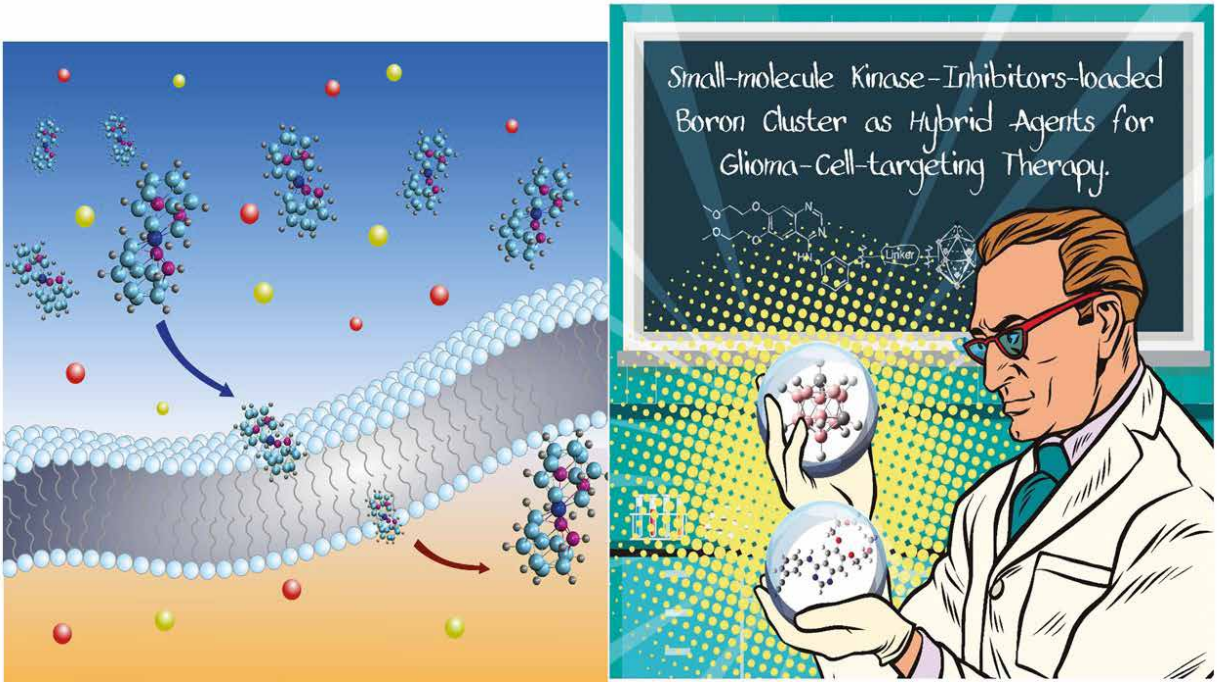
[3] M. Couto, C. Alamón, M.F. García, M. Kovacs, E. Trias, S. Nievas, E. Pozzi, P. Curotto, S. Thorp, M.A. Dagrosa, F. Teixidor, C. Viñas, H. Cerecetto. "Closo-carboranyl- and Metallacarboranyl[1,2,3]triazolyl-decorated Lapatinib-scaffold for Cancer Therapy Combining Tyrosine Kinase Inhibition and Boron Neutron Capture Therapy." Cells, 2020, 9, 1408; doi:10.3390/cells9061408; M. Couto, C. Alamón, S. Nievas, M. Perona, M. A. Dagrosa, F. Teixidor, P. Cabral, C. Viñas, H. Cerecetto. "Bimodal Therapeutic Agent against Glioblastoma, one the most Lethal Cancer". Chem.-AEur.J., 2020, 26, 14335–14340; C. Alamón, B. Dávila, M. F. García, C. Sánche, M. Kovacs, E. Trias, L. Barbeito, M. Gabay, N. Zeineh, M. Gavish, F. Teixidor, C. Viñas, M. Couto, H. Cerecetto. "Sunitinib containing carborane pharmacophore with ability to inhibit tyrosine kinases receptors, FLT3, KIT, and PDGFR-β, exhibits powerful in vivo anti-glioblastoma activity". Cancers, 2020, 12, 3423; doi:10.3390/cancers12113423; R.G. Teixeira, F. Marques, M.P. Robaloc, Xavier Fontrodona, M.H. Garcia, S. Geninatti Crich, C. Viñas, A. Valente. "Ruthenium carboranyl complexes with 2,2'-bipyridine derivatives for potential bimodal therapy application". RSCAdvances, 2020, 10, 16266-16276.

[4] E. Oleshkevich, A. Morancho, A. Saha, K. M. O. Galenkamp, A. Grayston, S. Gennatti Crich, D. Alberti, N. Protti, J. X. Comella, F. Teixidor A. Rosell, C. Viñas. "Combining Magnetic Nanoparticles and Icosahedral Boron Clusters in Biocompatible Inorganic Nanohybrids for Cancer Therapy". Nanomedicine, 2019, 20, 101986.

[5] K. J. Winberg, G. Barberà, L. Eriksson, F. Teixidor, V. Tolmachev, C. Viñas, S. Sjöberg. "High yield [125I-]-labeling of iodinated carboranes by palladium catalyzed isotopic exchange". J.Organomet.Chem., 2003, 680(1-2), 188-192; K. B. Gona, A. Zaulet, V. Gómez-Vallejo, F. Teixidor, J. Llop, C. Viñas. "COSAN as a molecular imaging platform: Synthesis and "in vivo" imaging". Chem.Commun., 2014, 50 (77), 11415–11417.

[6] I. Fuentes, J. Pujols, A. Singh, C. Viñas, S. Ventura, F. Teixidor. "Dual Binding Mode of Metallacarborane produces a robust shield on proteins". Chem.-AEur.J., 2019, 25, 12820–12829.

[7] I. Fuentes, T. García-Mendiola, S. Sato, M. Pita, H. Nakamura, E. Lorenzo, F. Teixidor, F. Marques, Clara Viñas. "Metallacarboranes on the road to anticancer therapies: cellular uptake, DNA interaction and in vivo evaluation of cobaltabisdicarbollide ([COSAN]-)". Chem.-AEur.J., 2018, 24, 17239–17254.



PL137

Loading tissues with heavy water to improv e beam penetration and better treat deeper tumours: revisiting an old idea in the modern era of accelerator BNCT

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The penetration of a typical epithermal neutron beam as produced from an accelerator BNCT system is not ideal for treating tumours that extend beyond 5-6 cm deep. Improved boron compounds with higher tumour or lower healthy tissue uptake would help greatly, and manipulation of the incident neutron beam spectrum might also be helpful. In this paper we will revisit the idea of loading the tissues with heavy water (D_2O) and discuss this in the context of a typical modern accelerator neutron beam.

This work follows that of Wallace et al [1], but is updated based on modern assumptions of boron concentration and CBE factor for BPA. We will also examine the sensitivity of results to changes in the assumed RBE for the neutron beam component since modern accelerator sources might warrant revision (and reduction) of the typically used value of 3.2.

Experience from adults treated with BNCT suggests that we need to be cautious regarding whole brain dose and peak dose to a region of healthy brain. In this study we have considered a peak weighted dose to healthy brain of 7 Gy which is similar to the doses proposed in recent studies from Taiwan treating children with BNCT[2].

We will present data which examines the benefits of D_2O loading for treatment of lesions in the brain. We will consider changes in

a) The proportion of D_2O in tissues, considering loadings of 0, 10 and 20%

b) The size of the patient head, including the typical range of paediatric patient head diameters

c) Changes in the boron concentration ratio between tumour and normal tissues including a reduced ratio of 2:1 (as seen from PET data in some of the patients treated recently in Taiwan) and an increased ratio of 20:1 as might be possible with a new prototype boron compound.

In order to assess the range of head sizes which should be considered, and to include a potential paediatric patient population, we have reviewed recent data from patients treated in Birmingham with radiotherapy. We measured the lateral "diameter" of the head (skin-to-skin) distance at the level of the centre of the tumour volume, and, for a posterior beam delivery, the depth from the skin surface to the deepest point of the tumour volumes. Results are summarised as follows:

- Lateral dimension: minimum 13.3 cm, maximum 16.0 cm
- Posterior depth: minimum 8.7 cm, maximum 12.1 cm

Results show that addition of D_2O suppresses the peak dose in healthy brain through changes to the neutron transport and reduced photon generation. At the same time the thermal fluence at depth is increased by an amount which increases with depth. This means that for a parallel-opposed beam configuration, the impact of D_2O loading is more pronounced for larger head diameters.

For a 12 cm diameter epithermal neutron beams incident in a parallel-opposed configuration onto an ellipsoidal water head phantom with diameter 16.5 cm, and with the usually assumed boron concentrations and RBE / CBE factors for BPA, results are shown in figure 1 below.

The key findings are as follows:

- For H_2O in brain, therapeutic ratio at brain centre reduces to just above 2:1 and a tumour here would receive a minimum dose of ~15.5 Gy weighted dose
- For 20% D_2O in brain, therapeutic ratio at brain centre remains always above 3:1 and a tumour at brain mid-line would receive a minimum dose of ~23 Gy.

Results for other boron concentration ratios and head sizes will be presented at the meeting.

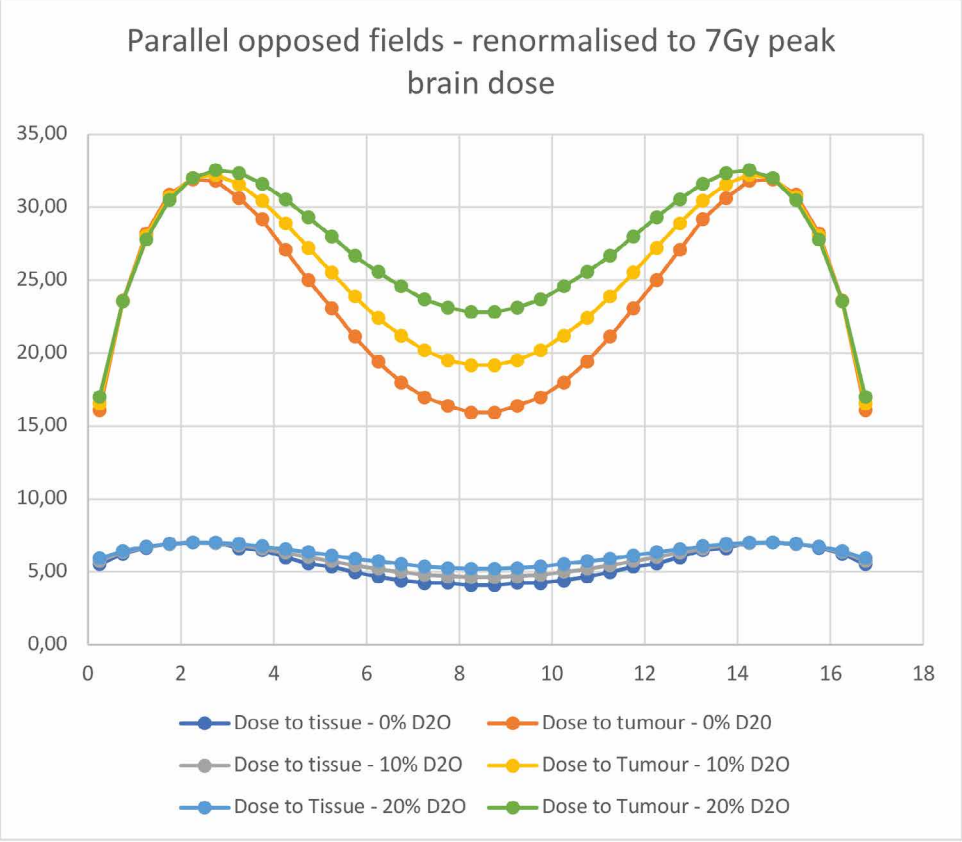

Figure 1: Parallel Opposed fields for 16.5 cm separation for "usual" BPA loading for adult GBM: Impact of D_2O loading

Keywords:
D_2O, heavy water, paediatric, brain

References:

[1] S A Wallace et al, 1995, *Monte Carlo calculations of epithermal boron neutron capture therapy with heavy water*, Phys. Med. Biol. 40 1599

[2] Jia-Cheng Lee et al, 2017, *Preliminary dosimetric study on feasibility of multi-beam boron neutron capture therapy in patients with diffuse intrinsic pontine glioma without craniotomy*, PLOS-one, https://doi.org/10.1371/journal.pone.0180461

Revisiting the age-old question: "Are photon-equivalent doses really photon- equivalent?"

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Twenty years ago, Coderre and collaborators from Brookhaven National Laboratory presented a work addressing the question "Are "photon-equivalent" doses really photon- equivalent?". In that work, the researchers recognized that BNCT doses in photon- equivalent units are based on a number of assumptions. They suggested that, by comparing the effects of BNCT in animal or biological models where the effects of photon radiation are known, it would be possible to test the validity of the assumptions and the accuracy of the calculated BNCT dose. This could also be achieved if there were endpoints reached in the BNCT clinical trials that could be related to the known response to photons of the tissue in question. Assuming that the high-LET components of the administered dose in BNCT can be multiplied by an experimentally determined fixed factor to adjust for the increased biological effectiveness, these researchers concluded that the resulting sum of the different radiation contributions, i.e., the photon-equivalent dose expressed in units (Gy-Eq), could be underestimated in normal brain, be adequate in skin and significantly overestimated in tumor.

Over the last decade, researchers have made efforts to understand the real scope of the question, and, consequently, to propose more suitable developments for translating BNCT doses into a photon radiation dose capable of quantifying clinical effects.

In this lecture, we will revisit this 20 year-old question in light of the photon iso-effective dose calculation formalism introduced in BNCT. We will begin by reviewing the concept of photon- equivalent dose, discussing the implicit assumptions and the underlying reasoning that allow us to make a formal description of the problem . We will then go through the models available for tumors and normal tissues developed under the different approaches, presenting their range of validity and recommendations. Taking as a guideline a clinical application of major interest in BNCT, we will exemplify the aspects that were taken into account for the choice of reference treatment and its conversion for comparison with BNCT. The validity and accurateness of the photon iso-effective dose calculations is discussed by comparing the effects of BNCT in patients with the effects of photon radiation. We expect the concepts and findings presented in this talk may shed some light on the age-old question.

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Current Status of Non-clinical trials Using Proton Linear Accelerator based Boron Neutron Capture Therapy System in Republic of Korea

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Since 2016, the development of Proton Linear Accelerator based Boron Neutron Capture Therapy (A-BNCT) system supported by Ministry of Trade, Industry and Energy (MOTIE) project has been started. Successful installation of A-BNCT system (10MeV, 8mA) has been finished at Songdo in Incheon in 2017. The capability of A-BNCT modality has been continuously improved depending on the escalated power and now we are performing non-clinical trials. Moreover, A-BNCT modality was selected as an innovative medical modality by Ministry of Food and Drug Safety honorably.

For the approval of BNCT system, variable non-clinical tests of each BPA, modality and combined tests of BNCT might be recommended inevitably. We evaluated BPA drug safety, pharmacology and stability tests and other required BNCT tests are in scheduled. The first requirements of *in vitro* and *in vivo* BNCT set-up are to validate methods of boron concentration by ICP-MS and dosimetry by simulation and measurements. The analysis of boron concentration in *in vitro* and *in vivo* sample tissues using ICP-MS and complex radiation measurements including neutron and gamma ray has been performed and the validation is in progress.

In vitro BNCT protocols include treatment methods in U87 and FaDu cell lines with treatment time, BPA concentration, number of cells, calibration curve, measurements of radiation dose, quality control and etc. Likewise, the experiments of *in vivo U87* xenograft tumor model revealed optimized irradiation time and duration depending on boron biodistribution of tissue and tumor after BPA injection time and dose. Now we are expecting *in vitro* and *in vivo* BNCT experiments using clinical beam quality corresponding to IAEA recommendations. After we finish all non-clinical trials for IND in 2021, we will start clinical trials in patients with brain tumor and head & neck cancer next year.

Current Status of the Xiamen Humanity Hospital-Neuboron BNCT Center and other BNCT Projects in Mainland China

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Xiamen Humanity Hospital (XHH) BNCT Center, located on the beautiful Xiamen Island city center, is the first BNCT clinical and research center built in China, which equips an accelerator-based BNCT (AB-BNCT) system, NeuPex™. The XHH project was first initiated in 2018, and broke the ground in May 2019. Through the difficult COVID-19 period, XHH BNCT Center has managed to successfully test its first epithermal neutron beam on the 5th August 2021, and the first animal experiment was performed in late August under GLP-like condition with Neuboron's GMP grade BPA. The system is now undergoing further commissioning, as well as validation and verification.

The AB-BNCT system NeuPex (model Block-I) was designed by Neuboron Medical Group to deliver epithermal neutron beam to maximum 3 treatment rooms (once per beam). The designed epithermal neutron beam could deliver a beam intensity of 1 x 10^9 epi. n cm^{-2} s^{-1} at the BSA (beam shaping assembly) beam port exit using a proton beam at 2.5 MeV and 10 mA (25 kW) and a solid, stational lithium target. An advanced, dedicated BSA made of high density MgF_2(LiF) and other moderator and reflector in a specially arranged geometry, is one of the very crucial roles of NeuPex. The epithermal neutron beam generated from the BSA could provide an advantage depth (AD) up to 11 cm (evaluated using Snyder phantom). The NeuPex was first tested using 27% theoretical nominal source intensity and a modified BSA, which successfully delivered a beam intensity higher than 3 x 10^8 epi. n cm^{-2} s^{-1} (further verification is now undergoing). The proton beam was driven by an electrostatic accelerator supplied by the TAE Life Sciences, which was designed to deliver a reliable proton beam at 2.5 MeV and 10 mA. The first test run was made at 2.3 MeV and 4 mA. The whole system is expected to reach its full performance late this year or early next year.

XHH BNCT Center will use the treatment planning system developed by Neuboron in house, named NeuManta (Neuboron Multifunctional Arithmetic for Neutron Transportation Analysis, NeuManta) with a dedicated Monte Carlo dose engine COMPASS (COMpact PAticle Simulation System, COMPASS). The treatment planning will be made using CT scan and PET images with F-BPA. Currently, the F-BPA clinical study is carried out in the Peking Union Medical College Hospital.

In addition to the XHH BNCT project, there are a few more BNCT projects on-going in Mainland China. One is the D-BNCT project in DongGuan City running by the Institute of High Energy Physics, Chinese Academy of Sciences. D-BNCT project utilized a 3.5-MeV RFQ proton accelerator and lithium target as the neutron source. The experimental machine has been built, and a new machine in under construction, which will be installed in the Dongguan People's Hospital. Another AB-BNCT project was proposed by the Lanzhou University using a RFQ accelerator too, and the prototype machine is under construction. Overall speaking, BNCT has received more

and more attention in China, and there are an increasing number of application and fundamental researches as well.

Keywords:
NeuPex, NeuManta, AB-BNCT, COMPASS

Clinical matters & new therapies

Clinical matters & new therapies

BNCT for Head and Neck Cancer: Relevance of N/C ratio and anti-tumor effect. -A preliminary report

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Introduction: BNCT is a type of particle beam radiation therapy that utilizes an α particle and ^{7}Li nucleus generated when a thermal neutron is captured by a ^{10}B nucleus involved in the boron compound that has been taken up into tumor tissue selectively. In this report, the relevance of N/C ratio of tumor cell and anti-tumor effect for BNCT clinical cases of head and neck cancer were verified.

Materials and Methods: We started clinical studies for the treatment of head and neck cancer in 2003. Examination of pre-irradiated tumor histopathological specimens of 9 BNCT treated head and neck cancer patients (4 CR patients, 5 non-CR patients) was performed. The statistically significant difference between the CR group and the non-CR group was examined for the following (1) and (2).

(1) Mean tumor dose of BNCT. This was calculated from the sum of the following doses: bioequivalent boron-neutron reaction dose, bioequivalent hydrogen-neutron and nitrogen-neutron reaction dose, and gamma ray dose

(2) Absolute biological effectiveness (ABE) dose: the physical dose was multiplied by the ABE value determined from the patient's tumor specific N/C ratio.

Results: Analysis showed the mean tumor dose could not distinguish between CR and non-CR groups. However, the ABE dose could clearly distinguish between the CR group and the non-CR group ($p = 0.0250$).

Conclusion: The N/C ratio of tumor cell can influence the anti-tumor effect of BNCT for HNC.

Keywords:
anti-tumor effect, N/C ratio, ABE dose, Head and Neck cancer.

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Salvage BNCT for recurrent malignant gliomas. Experience in Taiwan

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Tumor relapse is usually the final destiny for malignant gliomas although multidisciplinary treatment strategies are delivered aggressively. After recurrence, there is almost no other treatment choice and the treatment outcomes is dismal. Since March 2017, BNCT group in Taiwan started to use compassionate strategy (after approval by IRB of Taipei Veterans General Hospital and TFDA in Taiwan) for recurrent malignant glioma patients (Grade III-IV in WHO classification). Up to now (July 2021), we already help 70 patients complete salvage BNCT. Among these recurrent malignant glioma patients, we also recruited their treatment parameters of BNCT for analysis. We found that T/N ratio≥ 4, Tumor volume< 20 ML, mean tumor dose ≥ 25 Gy-E, MIB-1 index ≤ 40, and lower RPA class are good indicators for BNCT management. After analysis, we found for recurrent malignant glioma patients who already exhausted all treatment options maybe BNCT can be considered as a therapeutic approach to prolong their survival with good quality of life.

Keywords:
BNCT, recurrence, malignant glioma, radiotherapy, compassionate.

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Tumor 18F-BPA Uptake in PET as a Predictor for Tumor Response and Survival in a Patient Population Treated With BNCT for Locally Recurrent Head and Neck Cancer

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A high radiation dose from BNCT calculated based on constant tumor-to-whole blood boron concentration ratio is predictive for tumor response and favorable survival in patients with head and neck (H&N) squamous cell carcinoma [1]. Constant tumor-to-whole blood boron concentration ratio is often assumed in dose calculation. Alternatively, tumor-to-normal tissue (T/N) ratios obtained from the ^{18}F-BPA PET imaging prior BNCT have been used in dose calculations [2,3]. We investigated the association between the T/N ratios obtained from ^{18}F-BPA PET, doses calculated based on T/N ratio and efficacy of BNCT in patients with H&N cancer.

117 patients with inoperable, locally recurred H&N cancer were treated with L-BPA-mediated BNCT at the FiR 1 research reactor facility, Espoo, Finland, in February, 2003 to January, 2012 [1,4]. To estimate tumor BPA uptake, 33 patients underwent ^{18}F-BPA PET prior to BNCT. The T/N ratios were evaluated from static PET scans. On the BNCT treatment day, patient received 400 mg/kg of L-BPA-fructose as 2 h intravenous infusion. Blood boron concentration was measured from the blood samples with inductively coupled plasma atomic emission spectrometry. Normal tissue boron concentration was assumed to equal to that of the whole blood. Tumor dose was calculated assuming two different boron concentrations, 3.5 times that of the whole blood and according to the T/N in PET study. Tumor response to BNCT was assessed with CT and/or MRI imaging using the RECISTv.1.0 criteria.

Thirty-three patients (male, 55%) with squamous cell carcinoma (25, 76%), sarcoma (4, 12%), and adenocystic carcinoma (4, 12%) participated in the study. The median minimum radiation dose to the gross tumor volume (GTV), calculated with the measured blood boron concentrations and the T/N ratios from PET, was 14 Gy(W) (range, 7 to 78 Gy(W)), and when a constant tumor-to-blood ratio of 3.5 was assumed, 19 Gy (RBE) (range, 10 to 29 Gy(W)). Two patients were unevaluable for response to BNCT (died early). Nineteen (61%) of the 31 evaluable responded (had a CR or a PR). The median overall survival (OS) time estimate after BNCT was 22.8 months; 2-year OS was 42%. The ^{18}F-BPA PET-derived T/N values ranged from 1 to 18 (median, 2.7). The median OS for the patients who had a T/N ratio >2.7 was 12.3 months as compared to 27.7 months among those with a smaller ratio (log-rank p=0.036). A higher than the median T/N ratio did not predict for tumor response to BNCT (p=0.24).

A high tumor T/N ratio derived from ^{18}F-BPA-PET is associated with unfavorable survival after BNCT. Tumor dose calculated based on T/N ratio did not correlate with the response or survival. Cancers with high ^{18}F-BPA uptake in PET may often be biologically aggressive, which hypothesis requires further study.

Keywords:

^{18}F-BPA-PET, recurrent head and neck cancer, BNCT, dose response

References:

[1] Koivunoro H, et al. Radiother Oncol. 137: 153-158, 2019
[2] Suzuki M. et al. Journal of Radiation Research, 2014, 55, 146–153
[3] Wang L-W., et al. Int J Radiation Oncol Biol Phys, Vol. 95, No. 1, pp. 396e403, 2016
[4] Kankaanranta L. et al. Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1): e67-75.

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Boron Neutron Capture Therapy and Supportive and Palliative Care – Interesting Partnerships During the Pandemic

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Boron Neutron Capture Therapy has been largely used in patients who has disease which are refractory to standard therapies. Traditionally, such patients would have been referred to Palliative Care Services. There is a movement internationally where relevant interventions provided by Palliative Care Services are brought upstream in patients' disease trajectory to help alleviate symptoms. This is termed Supportive Care. Thus, it is inevitable that Boron Neutron Capture Therapy and Supportive and Palliative Care will cross paths. Such interactions between the two fields was more pronounced after travel restrictions were placed during the COVID-19 pandemic, especially in countries without BNCT facilities. We will describe our experience in Singapore with proposed solutions as to how we can move forward into a future where the restrictions we see today are likely to be the norm.

Keywords:
Boron Neutron Capture Therapy, Supportive and Palliative Care, COVID-19

Application of intra-tumoral injection of cationic polymers mixed with Gd compounds for Neutron Capture Therapy to pancreatic cancer model

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INTRODUCTION: The mortality rate of pancreatic cancer is very high, and 5years survival rate of pancreatic cancer are 16%, 1.2%, in stage2, stage4, respectively. We will perform the neutron capture therapy to pancreatic cancer in the intensive treatments [1]. It is necessary to increase the ^{157}Gd atoms in cancer cells, so we hope to apply the intra-tumors injection of ^{157}Gd compound. In clinically, we usually perform infra-tumoral injection by endoscopic ultrasound fine-needle aspiration (EUS-FNA) to diagnosis and injection of dendritic cell for immunotherapy. If we inject the ^{157}Gd solution, it will be easily go through away, and decrease the tumor concentration of ^{157}Gd atoms. So, we will apply the cationic polymers and fusion peptide mixing with ^{157}Gd compounds as like as we use in non-viral gene therapy. In this study, we evaluate the accumulating ability of cationic polymers, and tumor growth suppression by intra-tumoral injection of ^{157}Gd-cationic liposome complex (^{157}Gd-plex) with NCT.

METHODS: Experiment 1: Gadoteridol ($C_{17}H_{29}GdN_4O_7$; MW : 558.69) was used as ^{157}Gd compound. Polyethyleneimine (PEI) : ExGen 500(Fermentus Ltd) was used as cationic polymer. AsPC-1 human pancreatic cancer cells (2 x 10^6) were injected subcutaneously into the back of female BALB/c nu/nu mice. Gadoteridol solution (279.3 mg/ml) was mixed with PEI (15μ l) and prepared Gadoteridol mixed PEI complexes. After 2 weeks tumor inoculation, we perform intra-tumoral injection of 0.2ml of Gd-PEI complex or Gadoteridol solution to AsPC-1 tumor under anesthesia, and the Gd concentrations of tissues were determinated by prompt gamma spectroscopy of at Institute for Integrated Radiation and Nuclear Science, Kyoto University. **Experiment 2:** We prepared nanoparticles mixed with 1.5mL of Gadolinium compound "Gadovist" (MW: 604.71), 0.2mL of a solution of 10mg/mL-hyaluronic acid sodium, and 0.1mL of 20mg/mL of protamine incubating at room temperature for 30min. Then, these mixing solutions were poured into Cationic Liposome : Genetransfer (^{157}Gd-plex) [2,3]. We prepared AsPC-1(5x10^5) model by transplanting to right lower leg. Twelve hours after intra-tumoral injection of 0.2mL of ^{157}Gd-plex, we performed thermal neutron irradiation at Institute for Integrated Radiation and Nuclear Science, Kyoto University (1x10^{12} n/cm^2).

RESULTS : Experiment 1 : The retention effect of ^{157}Gd atoms was recognized by intra-tumoural injection using ^{157}Gd-PEI complexes in AsPC-1 tumors after 12hr administration. **Experiment 2 :** Tumor growth suppression was achieved in the ^{157}Gd-plex injected NCT group compared with non-irradiated group. The tumor growth suppression of the ^{157}Gd-plex injected group was superior than the only Gdovist injected group by NCT. These results showed that the cationic polymer are able to keep the ^{157}Gd atoms in the tumor tissue compared

with injection of only ^{157}Gd solution. It will be useful for increase the ^{157}Gd concentration in tumor for GdNCT. We will check the ^{157}Gd-plex to induce the endocytosis of ^{157}Gd atoms in cytoplasm or nucleus, and will modify to suitable complex.

CONCLUSION: We applied the cationoic polymer complexes to increase ^{157}Gd density by intra-tumoural administration for GdNCT. In the gadolinium delivery system using the cationic polymer complex, it is thought that I can apply it to second delivery of Gd atoms mixing in the WOW emulsion using the liver intra-arterial injection with double emulsification technique. We also hope to construct the ^{157}Gd-plex by authorized medical components, and will be proceed the early clinical study in future.

Keywords:
Drug Delivery System, Cationic polymer, Cationic liposome, Hyaluronic acid / Protamine complex, Intra-tumoral injection, Gadolinium Neutron Capture Therapy

Reference

[1] D. Novriana. J Cancer Res Clin Oncol. **2016**, 142:767-775.
[2] K. Maruyama. Biomaterials **2004**, 25:3267-3273.
[3] S. Harada. Biomed. & Pharmacother. **2015**, 70:196-205.

O129

The NECTAR project: first investigation steps to ascertain if NCT can be safely and effectively applied to treat Alzheimer's Disease

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NECTAR project (NEutron Capture enhanced Treatment of neurotoxic Amyloid aggRegates) has been recently funded by European Community H2020 framework, specifically within the FET- Open (Future Emerging Technology) RIA (Research and Innovation) action. The project consortium has the Physics Department of Pavia University as Coordinator and sees the participation of Italian, French, Swedish and German institutes and universities.

The aim of the project is to evaluate the feasibility, safety and effectiveness of NCT mediated by B-10 and/or Gd-157 to affect the neurotoxic aggregates of the beta-amyloid protein (A-beta), well known to be involved in Alzheimer's Disease (AD) pathology.

AD is the most common dementia and presently its treatment in mainly symptomatic and acts as palliation of cognitive functions decline. The aging of world population implies a higher number of patients and huge socio-economical costs, thus the investigation of other therapeutic strategies are very important.

AD is an amyloidosis associated to an abnormal production and reduced clearance of the A-beta protein which creates insoluble, neurotoxic aggregates following a progressive process: oligomers (spheres of few nm diameter) then packed into fibrils (few hundreds um chains of oligomers) which finally form senile plaques of few tens of um diameters. Despite the pathologic mechanisms triggering AD are still not clear and a huge debate about the central role of A-beta is underway, still oligomers has been recognised as the main neurotoxic species and the best correlation to disease severity [1]. Combining the typical mean dimensions of A-beta aggregates to the ranges of the charged secondaries of B-10 and Gd-157, NECTAR aims to evaluate if the high LET particles can depolymerise the aggregates and reduce their neuro-toxicity. In parallel, the presence of penetrating gamma rays in both the studied capture reaction will be investigated as a promoting factor of the A-beta clearance performed by glia cells.

The rational of NECTAR project heavily relies on the reported effectiveness of External Beam RadioTherapy (EBRT) of Tracheo-Bronchial Amyloidosis (TBA) and on the observation that both TBA and AD are amyloidosis characterised by specific pathological forms of proteins [2,3].

Until now, experimental studies have been made in vitro and in vivo on murine AD models: the first shows no major differences between irradiated and non-irradiated samples [4]; the latter, instead, shows a significant reduction in Aβ plaques and minimal effects on the brain, in particular no cognitive deficit [5].

The talk will present the preliminary studies carried out at Pavia University, in particular focusing on Monte Carlo simulations (using PHITS and MCNP codes) and related to: (i) microdosimetric estimation of the energy deposited in the different A-beta aggregates when protein water solutions are irradiated at the thermal facilities available at Pavia reactor and (ii) preliminary macroscopic estimation of the effects (mean doses, whole body neutron-induced activation) of such irradiations in AD transgenic mice.

Keywords:
NCT, B-10, Gd-157, Alzheimer's Disease, brain irradiation

References:

[1] Balducci et al., PNAS, 107:2295-2300 (2010).
[2] Nebe-Wittich et al., Chest, 132(1):262-267 (2007).
[3] Bistolfi, The Neurol J 21:683-692 (2008).
[4] Patrias et al., Rad Res 175:375-381 (2011).
[5] Marple et al., Radioth Oncol 118:43-51 (2016)

Clinical trial of Accelerator-based BNCT for Cutaneous Melanoma and Angiosarcoma

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The National Cancer Center (NCC), Japan started the program of accelerator-based boron neutron capture therapy (BNCT) in 2010. Under the joint research collaboration with NCC and CICS Inc., we developed an accelerator-based neutron irradiation system for BNCT with a solid lithium target. The system was installed in the area of the Department of Radiation Oncology, National Cancer Center Hospital in 2014. Physical measurements and biological experiments have been performed since 2016, and after consultations with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), a phase I clinical trial of BNCT for cutaneous melanoma and angiosarcoma started in November 2019. We use borofalan (^{10}B) (boronophenylalanine, BPA; SPM-011, Stella Pharma) as the boronated drug for BNCT.

The neutron irradiation system we have developed was the first in the world to be used clinically for BNCT with a solid lithium target. Through this clinical trial and upcoming further clinical trials, we are aiming the goals shown below: (1) to get the approval of our neutron irradiation system as a medical device by authorities; (2) to prove the safety and efficacy of BNCT for melanoma and angiosarcoma; (3) to obtain expanded indications of borofalan (^{10}B) for melanoma and angiosarcoma in Japan by authorities; (4) to determine the maximum tolerable dose of irradiation to the skin by BNCT.

We will introduce the clinical trial of BNCT for cutaneous melanoma and angiosarcoma, including our neutron irradiation system and the achievements to date concerning the development of BNCT within this presentation.

Clinical matters & new therapies

Poster

Title of your abstract: Calibration and validation of thermoluminescent dosimeters for thermal neutron flux measurement

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Purpose:

A new method using TLD-600 and TLD-700 was proposed to measure a thermal neutron flux, which is used to evaluate ^{10}B and ^{14}N doses for boron neutron capture therapy (BNCT).

Material and method:

TLD reading

The TLD-600 and TLD-700 (Harshaw, USA) chips were prepared for this study. Its diameter was 4.5 mm and the thickness was 0.6 mm. The TLDs used in this study are lithium fluoride based materials (LiF:Mg,Ti). TLD-600 was enriched by 6Li (95.6%) whereas TLD-700 was enriched by ^{7}Li(99.99%) [1]. Due to the difference in neutron cross-section of ^{6}Li and ^{7}Li, TLD-600 is sensitive to neutrons and TLD-700 is insensitive to neutrons [2]. The TLDs were annealed with an electric furnace at 400ºC for 1 hour followed by 100ºC for 2 hours to eliminate the residual signals before the irradiation. The readout of TLDs was done by using Harshaw TLD reader (Model 3500). The TLDs were linearly heated from 50 ºC to 300 ºC at 10 ºC/sec. The acquisition time was 33.3 seconds. The TL signal was converted in the unit of electric charges by integrating the glow curves from channels 72 to 200. The thermal neutron induced TL signal was separated by using the combination of TLD-600, TLD-700 and cadmium sheets with their different interaction probabilities of neutrons and gamma rays.

TLD calibration factor

The TLDs were calibrated using a ^{252}Cf neutron source within a 30 cm-diameter D_2O sphere to produce the thermal neutron flux calibration factor. The calibration factor was obtained by dividing the neutron-induced TLD readings by the Wescott fluence. The neutron self-shielding correction was calculated to compensate for the perturbed neutron fluence in TLDs.

TLD validation

To evaluate whether the calculated TLD calibration factor is valid, a research/educational reactor, known as a thermal neutron source, was used. The thermal neutron flux measured through the applying calibration factors of TLDs was compared with the thermal neutron flux using the conventional gold wire activation method. At this time, the thermal neutron flux is the Westcott fluence.

Results and discussion:

The evaluated TLD calibration factor was 3.80×10^4 $cm^{-2}nC^{-1}$. The thermal neuron flux at the reactor was 2.28×10^5 $cm^{-2}W^{-1}s^{-1}$ by the TLD method and 2.17×10^5 $cm^{-2}W^{-1}s^{-1}$ by the gold activation method. The difference in the thermal neutron fluxes was 5%. With the thermal neutron fluence measured by TLDs, D_{TLD} can be calculated. Then the two major components of BNCT dosimetry, $D_{B\text{-}10}$ and $D_{N\text{-}14}$ can be calculated by multiplying D_{TLD} with constants. Table. 1 shows the results of validation of TLDs at the reactor. In 4 measurements, when the thermal neutron flux was normalized to the reactor power and irradiation time, the average value was 2.28×10^5 $cm^{-2}W^{-1}s^{-1}$. The thermal neutron flux measured by TLD showed an average difference of 5%.

Conclusions:

The TLD method developed in this study was successfully validated against an unknown mixed neutron/gamma field from the reactor, showing about 5% difference in measured thermal neutron fluences when compared to the conventional gold activation method. Therefore, the two major dose components of BNCT, ^{10}B and ^{14}N doses can be accurately evaluated by the neutron-induced TLD dose.

Irradiation	**#1 (2W, 0.5 h)**	**#2 (2W, 0.5 h)**	**#3 (4W, 0.5h)**	**#4 (4W, 0.5h)**
Thermal neutron induced signal (nC)	6720.67	6396.22	13873.72	13573.92
Calibration factor [cm^{-2} nC^{-1}]	**3.8×104**			
Thermal neutron flux (Wescott) [$cm^{-2}s^{-1}W^{-1}$]	2.29×10^5	2.18×10^5	2.36×10^5	2.31×10^5
	Gold wire: 2.17×10^5			
Relative difference [Flux TLD / Gold]	**1.05**	**1.004**	**1.08**	**1.06**

Table 1. The results of validation of TLDs at the reactor.

Keywords:
thermoluminescent dosimeter, boron neutron capture therapy, dosimetry, gold activation analysis

References:

[1] Model 3500 Manual TLD Reader With WinREMS, Operator's Manual, Thermo Scientific. 2010.
[2] D.A. Brown, et al., ENDF/B-VIII. 0: the 8th major release of the nuclear reaction data library with CIELO-project cross sections, new standards and thermal scattering data, Nuclear Data Sheets, 148, p. 1-142. 2018.

Clinical experience with two-field neutron irradiation of high-grade meningiomas with patient repositioning in single machine time

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Introduction

Boron neutron capture therapy (BNCT) is a tumor-selective therapy that utilizes the boron neutron capture reaction. Our research group has shown the effectiveness of BNCT in several clinical trials for malignant gliomas and meningiomas. Meningiomas are generally originated from arachnoid cap cells or meningothelial cells at relatively superficial just below the skull. However, some meningiomas which arise from deep regions on the cerebral falx or base regions of the skull are difficult to treat completely because there are many structures which must be preserved, such as blood vessels and nerves. High-grade meningiomas classified as WHO grade II or III shows not only histopathological aggressive but also invasive nature into the normal brain tissue, extensively growing along the dura mater or relapse in the form of multiple lesions. Therefore, high-grade meningiomas are refractory to repeated surgery and radiotherapy. In this study, we focused on our experiences with two-field neutron irradiation at BNCT for extensive, deep or multiple lesions in recurrent high-grade meningiomas.

Methods [1, 2 ,3]

BNCT was conducted on several cases of recurrent high-grade meningiomas with neutron irradiated at a reactor power of 5 MW with the Heavy Water Neutron Irradiation Facility in the Institute for Integrated Radiation and Nuclear Science, Kyoto University. Boronophenylalanine (BPA) which had been used in clinical trials for malignant gliomas was used. Among the patients irradiated from 2005 to 2018, the patients who were irradiated by two-field were selected in order to analysis. Two-field irradiation was performed during continuous administration of BPA. After the first irradiation, the patient position was re-set up and the second irradiation was performed. As in the case of single-irradiation, the irradiation time was calculated from the total dose irradiated twice. Specifically, the total dose was adjusted by the irradiation time, which was calculated from the blood boron concentration and the calculated total dose to normal tissue in the two-field irradiation. The maximum dose was defined on the basis of the tolerable dose in normal brain or skin / mucosal tissues.

Results

Two-field irradiation was planned for eight treatments. The irradiation times were 40 ± 11 minutes for the first irradiation and 35 ± 9 minutes for the second irradiation. The irradiation interval was 37 ± 4 minutes. There were two cases in which the second irradiation was interrupted or discontinued. Tumor localization consisted of extensive lesions, deep-seated lesions or multiple lesions. All cases experienced treatment-related adverse events (AEs) within 1 month, including increased amylase, fever, lymphocyte count decreased and so on. Salivary gland amylase was mainly increased and improved immediately with follow-up. Within the following 6 months, most AEs had been improved except for alopecia. We also experienced the cases of brain edema.

Discussion

Since two-field neutron irradiation reduces the dose to normal tissues and allows irradiation of multiple sites, we thought that it would also ensure tumor dose to deep -seated lesions, such as skull base location, and allow irradiation of large areas or even multiple lesions in single machine time. Because these AEs were similar to those of BNCT for malignant gliomas, these results suggest the safety of two-field neutron irradiation with extended continuous BPA administration during treatment.

Conclusion

Although various doses of BPA have been used in previous clinical trials, this irradiation method suggests that extended continuous BPA administration to allow two-field irradiation at single machine time with patient repositioning may not results in serious AEs. When not only high-grade meningiomas but also intracranial brain tumors may require two or more multiple field irradiation, this method may provide a basis for accepting various irradiation protocols for BNCT.

Keywords:
high-grade meningioma, two-field irradiation, BPA

References:

[1] Takeuchi K, Kawabata S, Tanaka H, Suzuki M, Miyatake SI, et al. J Neurol Surg B Skull Base. 2018; 79 (Suppl 4): S322-S327.
[2] Kawabata S, Miyatake S, et al. J Neurosurg. 2013; 119(4): 837-844.
[3] Miyatake S, Kawabata S, et al. Neurosurgery. 2007; 61(1): 82-90.

BNCT for cutaneous melanocytoma with *CRTC1-TRIM11* fusion

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[Introduction]

Cutaneous melanocytoma with *CRTC1-TRIM11* fusion (CMCT), a new tumor entity, is a pigmented tumor of the skin proposed by Cellier et al. in 2018 [1]. To date, only 11 cases have been reported; however, many aspects such as its similarity to soft tissue clear cell sarcoma (CCS) and its malignant potential are unclear. Here, we describe the first application of BNCT to CMCT.

[Case]

A 24-year-old woman with a gradually growing soft tissue mass in her left heel for two years was referred to our hospital. A well-defined, elastic-hard mass, 3 cm in diameter, with tenderness was detected in the subcutis. Histological examination of a needle biopsy revealed that ovoid tumor cells were arranged in cellular nests like CCS. They possessed round nuclei with a prominent nucleolus and clear to eosinophilic cytoplasm. Fluorescence in situ hybridization (FISH) did not show EWSR1 rearrangement. Since the *CRTC1-TRIM11* fusion gene was detected through RT-PCR, the diagnosis of CMCT was reached. FBPA-PET/CT demonstrated tumor-selective uptake of ^{10}B (SUVmax 4.07, T/N ratio 5.58), and immunohistochemical studies disclosed strong expression of L-type amino acid transporter 1 (LAT1), which incorporates BPA into tumor cells through tumor cell membranes. No metastasis was found on FDG-PET/CT, and tumor resection with a wide margin was planned; however, BNCT was implemented because the patient preferred non-invasive treatment first. At BNCT, an irradiation dose of more than 37 Gy-Eq was applied to the whole tumor, but no shrinkage of the mass was observed in imaging studies. Concluding, therefore, that BNCT imparted no antitumor effect, a two-stage surgery was carried out. First, the tumor was simply resected to preserve the normal tissue as much as possible. Second, after confirming by histopathological examination the R0 resection, reconstructive surgery was carried out with a pedicled skin flap. Histopathological studies of the resected specimen demonstrated the same histological features as those of the

biopsy, indicating no or minimal therapeutic effects on tumor cells by BNCT. No recurrence or metastasis of the tumor has been observed one year after surgery.

[Discussion]

CMCT is considered a tumor different from CCS, with a unique fusion gene, *CRTC1-TRIM11*; however, its histological and immunohistochemical characteristics are very similar to those of CCS [2]. Furthermore, imaging studies with FBPA-PET/CT showed high uptake of BPA by the tumor, and immunohistochemical studies showed specific LAT1 expression on tumor cell membranes as in CCS, for which BNCT has been reported to be effective [2]. Based on these data, BNCT was administered to the present case of CMCT, but no antitumor effect was observed. The malignant potential is different between CMCT and CCS. CMCT seems to be less malignant than CCS. Although CMCT cases reported were still few, only one case was described to show metastasis. In addition, a very low Ki-67 labeling index indicated low-proliferative activity of tumor cells of CMCT. The low-proliferative activity may be related to low uptake of BPA as a whole. Consequently, even if the evaluation by FBPA-PET/CT is high, it is assumed that BNCT may not be effective for CMCT. Further studies are needed on the relation between the antitumor effect of BNCT and the cell proliferation ability of tumors.

Keywords:
BNCT, cutaneous melanocytoma with *CRTC1-TRIM11* fusion, clear cell sarcoma, resection, FBPA-PET/CT, Ki-67, LAT1

References:

[1] Cutaneous Melanocytoma With *CRTC1-TRIM11* Fusion: Report of 5 Cases Resembling Clear Cell Sarcoma. Cellier L et al., Am J Surg Pathol. 2018; 42:382-391.
[2] Boron neutron capture therapy for clear cell sarcoma. Fujimoto T et al., Appl Radiat Isot. 2020; 166:109324.

New Perspectives for Neutron Capture Radiation Therapy with 7Be and 22Na: Advantages and Bottlenecks

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The neutron capture radiation therapy (NCT) of cancer can be potentially much safer and can offer a better spatial and temporal control than the radioisotope therapy. Still, there are not many options in NCT: 10B isotope has been almost exclusively used for decades, and only relatively recently, 157Gd has attracted some interest. Due to the recent developments of compact accelerators for the neutron production and of the drug delivery methods, there is a growing interest in NCT worldwide coming to hospital-based facilities. We have identified recently [1] two other nuclides potentially suitable for the NCT which have ca.10 times larger cross section of absorption for neutrons and emit heavy charged particles. This would provide several key advantages for potential NCT, such as the possibility to use a lower nuclide concentration in the target tissues, or a lower neutron irradiation flux. By detecting the characteristic radiation from the spontaneous decay of the radionuclides, one can also image their biodistribution.

We will present and discuss these advantages which can be critical to bring the NCT to a safer, targeted, and personalized cancer theranostics, including the possibility of hybrid (e.g., Be/B/Gd) NCT. Also, we will discuss the obstacles in this challenging way and the potential approaches to overcome them [2]. In particular, we have identified three major necessary advancements to be made in order to progress in the BeNCT technology:

Confinement. Beryllium is known for its high chemical toxicity (LD50 for animals ca. 10 mg/kg). This is due to Be2+ high affinity for oxygen donors, particularly water, which results in the formation of very stable hydrolysis products and in the hydroxide precipitation above pH 3 and 5, respectively. From a biochemical point of view, Be2+ has the ability to displace protons in strong hydrogen bonds, and, in general, Be2+ can strongly interact with carboxylate and phosphate groups of many different biomolecules, thus altering their physiological function. Therefore, it is fundamental to identify stable, hydrosoluble and nontoxic compounds/systems for isolation (via chemical coordination or encapsulation) of Be2+, capable to prevent the formation of the hydrolysis products and to fully entrap Be2+ in order to hinder its unwilled interaction with biomolecules.

Selective accumulation. In order to obtain the required absorbed radiation dose in the tumor and minimize the adverse effect on the healthy tissues, the 7Be concentration in the tumor tissue should be few ppm (micrograms per gram of tumor) [1], i.e. app.10 times smaller than that required in BNCT. The concentration ratio in the cancer cells to that in the surrounding healthy tissues must be at least 3:1. Thus, it is crucial to functionalize the beryllium-containing compounds to target specific tissues.

Biological radiation effect. The main ionizing particles after the neutron capture decay are different for the 10B/157Gd and for the 7Be (α-particles/Auger electrons vs protons), so that the biological effect is expected to be different at the same total kinetic energy. In particular, the proton has a longer range in tissues than α-particles, which allows it to cross several cells and increase the probability to hit the target cell nucleus, although with lower LET [1]. Thus, it is necessary to experimentally determine the biological effect of the BeNCT vs. BNCT at the same concentration of the active nuclide and at different values of the neutron energy and flux.

References:

[1] Kukulin V.I., et.al. // arXiv:1907.05934 [physics.med-ph]
[2] M.A.Scorciapino, et.al. // J. Nanosci. Nanotechnol. 21, 2939–2942 (2021)

Neutron sources & facilities

Neutron sources & facilities

Present Status of Accelerator-Based Neutron Sources for BNCT

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Accelerators have become the primary source of epithermal neutrons for clinical BNCT. Several accelerator-based neutron sources (ABNS) are commercially available or under development. Most existing or planned systems make use of either the $^{7}Li(p,n)^{7}Be$ reaction or the $^{9}Be(p,n)^{9}Be$ reaction to generate neutrons, although other reactions have been considered [1]. The former requires a proton accelerator with energies between 1.9 and 3.0 MeV while the latter typically requires accelerators with energies between 5 and 30 MeV. Aside from lower required proton energy, the main benefit of the $^{7}Li(p,n)^{7}Be$ reaction is lower energy of the neutrons produced. This allows smaller moderators, "cleaner" neutron beams, and reduced neutron activation. Benefits of the $^{9}Be(p,n)^{9}Be$ reaction include simplified target design and disposal, longer target lifetime, and a lower proton beam current.

Since the proton beams for BNCT are quite powerful (~20-100kW) the neutron generating target must incorporate cooling systems capable of removing the heat safely and reliably in order to protect the target from damage. In the case of lithium, this requirement is especially important due to the low melting temperature and chemical volatility of the target material. Liquid jets, micro-channels and rotating targets are employed to solve this problem. Several researchers have proposed the use of liquid lithium targets in which the target material doubles as the coolant [2,3]. In the case of beryllium, "thin" targets, in which the protons come to rest and deposit much of their energy in the cooling fluid can be employed. Target degradation due to beam exposure ("blistering") is another problem to be solved, either by using layers of materials resistant to blistering or by spreading the protons over a large target area.

Since the nuclear reactions yield neutrons with energies ranging from <100keV to 10's of MeV, a Beam Shaping Assembly (BSA) [4] must be used to moderate, filter, reflect and collimate the neutron beam in order to achieve the desired epithermal energy range, and neutron beam size and direction. BSAs typically are composed of a range of materials with desirable nuclear properties for each function. A well-designed BSA should maximize the neutron yield per proton while minimizing fast and thermal neutron and gamma contamination. It should also produce a sharply delimited and a generally forwardly directed beam permitting flexible positioning of the patient relative to the aperture. [5]

One key challenge for an ABNS is the duration of treatments. Depending on the neutron beam intensity, treatments can take up to an hour or more. Therefore it would be advantageous to reduce the treatment time both for patient comfort during immobilization and to increase the number of patients that can be treated per day. Increasing the neutron beam intensity for the same proton current by adjusting the BSA is often achieved at the cost of reduced beam quality, such as higher levels of unwanted fast neutrons or gamma rays in the beam or poor beam collimation. Therefore, increasing the proton current delivered by ABNS BNCT systems remains a key goal of technology development programs. Finally, as part of this presentation, a summary of current and planned accelerator based neutron sources worldwide, and their general characteristics will be discussed.

Keywords:
Neutron Sources, Accelerators, ABNCT

References:

[1] Kreiner, A. J., Bergueiro, J., Cartelli, D., Baldo, M., Castell, W., Asoia, J. G., ... & Tacca, H. (2016). Present status of accelerator-based BNCT. *Reports of Practical Oncology & Radiotherapy*, *21*(2), 95-101.
[2] Paul, M., Silverman, I., Halfon, S., Sukoriansky, S., Mikhailovich, B., Palchan, T., ... & Barami, E. (2020). A 50 kW Liquid-Lithium Target for BNCT and Material-Science Applications. In *EPJ Web of Conferences* (Vol. 231, p. 03004). EDP Sciences.
[3] Kobayashi, T., Miura, K., Hayashizaki, N., & Aritomi, M. (2014). Development of liquid-lithium film jet-flow for the target of 7Li (p, n) 7Be reactions for BNCT. *Applied Radiation and Isotopes*, *88*, 198-202.
[4] Uritani, A., Menjo, Y., Watanabe, K., Yamazaki, A., Kiyanagi, Y., & Tsuchida, K. (2018). Design of beam shaping assembly for an accelerator-driven BNCT system in nagoya university. In *Proceedings of the International Conference on Neutron Optics (NOP2017)* (p. 011002).
[5] Coderre, J. (2001). IAEA-TECDOC-1223.

Current Beam Performance of iBNCT001, the demonstrator of a linac-based BNCT device in University of Tsukuba

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University of Tsukuba is going to promote the iBNCT project, which consists of industry-academia-government collaboration teams KEK, the project is developing iBNCT001 as the demonstration device of a linac-based BNCT device. iBNCT001 has adopted a linac consisted of an RFQ and a DTL and has been combined with beryllium of 0.5 mm thick as neutron target material. The linac has designed to accelerate protons of 5 mA or more to 8 MeV and currently the iBNCT001 has succeeded to drive with an average proton current of 2.1 mA. At present, beam aperture of 120 mm in diameter has been installed at the end point of the beam collimator. In the condition, epithermal neutron flux at the center of the beam aperture is approximately 8×10^8 (n/cm^2/s) in calculation. Several beam apertures like 150 mm in diameter have been prepared and can be changed.

To confirm the applicability of the iBNCT001 to BNCT, we are conducting several characteristic measurements. In the experiments with a rectangular water phantom, distributions for thermal neutron flux and gamma-ray dose rate, which are the fundamental elements of BNCT dosimetry, were measured. In the evaluation for thermal neutron flux distribution, we applied the activation foil method. The water phantom including pure gold wires was irradiated and then the activities of each gold wire were measured. For the measurement for gamma-ray dose distribution, thermoluminescent detector (TLD) was used. When the device emitted epithermal neutrons while operating the linac with an average current of 2.1 mA, the maximum thermal neutron flux in a water phantom was approximately 1.4×10^9 (n/cm^2/s) at 2 cm in depth on the central axis in the phantom. The neutron intensity has sufficient performance to complete irradiation within 30 minutes with BNCT for head and neck cancer and malignant brain tumors. The maximum gamma-ray dose rate in the phantom in the same beam condition was approximately 5.0 Gy/h at around 2 cm in depth. Figure 1 shows both distributions for thermal neutron flux and gamma-ray dose rate on the beam axis.

To confirm the reliability of the linac, the 60 min. continuous driving has been performed repeatedly, and then the success rate of the continuous operation was achieved 90% or more. Furthermore, to confirm the safety and the practicability in the irradiation with actual patients, leakage radiations were also estimated. When the neutron beam was released from the beam aperture in free-in-air condition, neutron intensity and gamma-ray dose rate on the wall outside beam aperture were measured. And to determine radiation exposure with a patient during treatment, irradiation experiments using a whole-body phantom positioned to irradiation position were performed, and then neutrons and gamma-ray dose rate at several points on the phantom such as chest and abdomen were measured. The doses for each point in the whole-body phantom were also determined by simulating the irradiation experiment with a Monte Carlo transport calculation and the results were normalized by the measurement values.

We plan to also measure the beam characters for the combination with other beam apertures such as a circular shape of 150 mm in diameter and protruded beam collimators. When the physical characteristic measurements are finished, we will implement immediately non-clinical studies with the irradiations for cells and mice with the iBNCT001.

Keywords:
BNCT, accelerator-based neutron source, beryllium, phantom irradiation

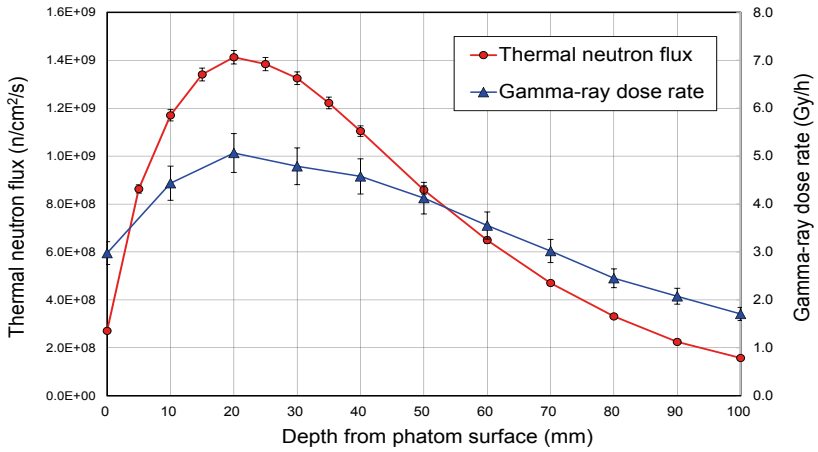

Fig.1 Distributions for thermal neutron flux and for gamma-ray dose rate on beam axis in the rectangular water phantom.

Accelerator-based BNCT system in Nagoya University –Project status 2020 –

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Nagoya University

1. Introduction

An accelerator-based neutron source with a combination of high power accelerator and Li target is very advantageous for Boron Neutron Capture Therapy from a neutronic point of view. At Nagoya University, we have been developed a sealed Li target with a unique structure and have been performing accelerator-based BNCT system project.

2. Dynamitron Accelerator

A DC accelerator (Proton-Dynamitron, IBA) with a proton energy of 2.8 MeV and a maximum current of 15 mA was introduced in 2015. The proton beam trajectory is controlled by the three quadropole magnets and a set of the steering magnet. To estimate the spatial variation of the beam size over the beamline, a beam transport analysis was performed by a linear optics model (the 6 by 6 thick lens quadrupole model). In 2020, we have achieved in transporting a high-current beam of 8 mA by using a beam analysis model in combination with experiment results. In addition, a beam scanning system was introduced to reduce the heat load on the target, we succeed in expanding the beam irradiation area.

3. Sealed Li Target

A unique developed sealed Li target has a structure in which Li metal settled on a cooling plate is covered with Ti foil. In previous studies, high heat removal efficiency could be achieved by inducing turbulent flow by developing a ribbed cooling water channel [1]. The basic design and production of the sealed Li target structure have been completed, and the endurance test by proton beam irradiation is currently being conducted. No damage was observed on Ti foil after proton beam irradiation with beam power density of 5.7 MW/m^2 for a total 50 hours [2].

4. Beam Shaping Assembly (BSA)

A BSA of Nagoya system has a unique system with a nozzle for compact gantry system. Previous designs and preliminary experiments have present that the neutron field emitted from the nozzle conforms to the IAEA-TECDOC-1223 [3][4]. Improvement in BSA and nozzle lead to more therapeutically suitable neutron generation.

5. Neutron measurement experiments

The spatial distribution of the thermal neutron in the water phantom was measured by the gold foil activation method. The current of the proton beam used in the experiment was 4mA. The thermal neutron flux was evaluated to be 2.5 x 10^8 $n/cm^2/s$ at a distance of about 20 mm from the beam incident surface of the water phantom.

References

[1] S. Yoshihashi, et al.,Hgh heat technique for a lithium neutron generation target used for an accelerator-driven BNCT system, Journal of Instrumentation, to be published.
[2] S. Honda, et al.,Development of a sealed lithium target for BNCT in Nagoya University, Abstrace of 19th international congress on neutron Capture therapy.
[3] K. Sato, et al.,Improved dsighn of the exit of a beam shaping assembly for an acceleraor-driven BNCT system in Nagoya University, JPS Conf. Proc., 22, 011003(1-7), 2018.
[4] K. Watanabe et al., First expetimental verification of the neutron field of Nagoya University Accelerator-driven neutron source for boron neutron vapture therapy, Applied Radiation and Isotopes, 168, 2021.

A study on non-primary radiation of an accelerator-based BNCT neutron beam

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The recommendation for epithermal neutron beam for boron neutron capture therapy has been focused on the beam characteristics at the beam port, such as the in-air beam intensity and quality, and the in-phantom figure-of-merits. In the recent Virtual Technical Meeting on Advances in Boron Neutron Capture Therapy held by IAEA on July 27-31 2020 [1], the issue of the out-of-field leakage in boron neutron capture therapy was addressed, and the recommended values for the ambient dose equivalent from neutrons/photons for distance 15-200 cm from the beam edge were proposed. The proposed recommended value for the ambient dose equivalent from neutrons is < 5 mSv/Gy-w for distance 15-200 cm from the beam edge, and for the ambient dose equivalent from photons is < 5 mSv/Gy-w for distance 15-50 cm from the beam edge, < 1 mSv/Gy-w for distance 50-200 cm from the beam edge.

Heron Neutron Medical Corporation has been working on the beam design for an accelerator-based BNCT facility. In this study an ORNL MIRD mathematical phantom is used to calculate the whole-body dose associated with the BNCT treatment of head-and-neck cancer. The beam profile and the ambient dose from the beam edge are also calculated.

In the whole-body dose calculation, instead of equivalent dose, RBE factor is used to obtain the RBE-weighted dose of individual organ. Then, tissue weighting factor is used for obtaining the whole-body dose. The incident direction of neutron beam is from the left-hand side of the mathematical phantom with a lying posture, aiming at the center of the brain. The left shoulder is aligned with the surface of the beam exit. The irradiation time is the time required to give 20 Gy-w for 80 % of the tumor volume. The RBE weighted dose of abdomen region is < 40 mGy-w, close to the regulatory dose limit 30 mGy for the computed tomography scan for diagnostic purpose. The whole-body dose is 134 mSv, among which, ~ 40% of the dose comes from the 14 cm diameter beam port, and ~ 65% from the extended beam port region with 22 cm diameter.

On the other hand, the calculated value of ambient dose equivalent from neutrons of our beam design is 16 mSv/Gy-w at distance 15cm from the beam edge, < 5 mSv/Gy-w for distance 30-200 cm from the beam edge. The beam profile shows that the neutron ambient dose drops to <1/10 of the central value at distance 15cm from the beam edge. The calculated value of ambient dose equivalent from photons is < 1 mSv/Gy-w at distance 15 cm to 200 cm from the beam edge.

Although the out-of-field leakage of our beam design is higher than the tentatively proposed guideline, the whole-body dose, however, is reasonably low. The whole-body dose calculation along with the beam profile analysis can be helpful in reaching an acceptable recommendation for the non-primary radiation for BNCT neutron beam.

Keywords:
whole-body dose, non-primary radiation, beam design

References:

[1] Hanna Koivunoro et. al., "Out-of-field leakage in boron neutron capture therapy", Virtual Technical Meeting on Advances in Boron Neutron Capture Therapy, EVT1905174, IAEA, July 27-31 2020.

Architecture, Implementation, and First Performance Results of a Neutron Beam System for Accelerator BNCT

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Accelerator-based boron neutron capture therapy (BNCT) requires simple, reliable, and cost effective sources of neutron beams. Proton-lithium reaction at proton energies of about 2.5MeV generates neutrons with energy spectrum favorable for BNCT. This range of proton energies is optimal for electrostatic accelerators. Modern technologies of electrostatic accelerators make it possible to achieve the targeted performance and meet the requirements of reliability, simplicity, and cost.

The tandem type of electrostatic accelerators is particularly attractive for the Neutron Beam System (NBS) for accelerator BNCT. The principle of operation of tandem accelerators makes it possible to reduce the accelerating voltage by a factor of two, and to place the ion injector at the ground potential. The first implementation of an experimental tandem accelerator for BNCT NBS was developed at the Budker Institute of Nuclear Physics (BINP), which has partnered with TAE Technologies to commercialize the technology by increasing the nominal proton beam energy and current to clinically relevant levels.

In order to boost the proton beam parameters, the architecture of the tandem accelerator underwent substantial improvements, including the replacement of the Cs-based negative ion source with a Cs-free alternative. Introduction of a pre-accelerator, together with advanced beam optics, helped to resolve long-standing issues with current limitation and beam stability in the tandem. The design of the high voltage power supply was improved to achieve high reliability. The adaptive high energy beam line provides high uniformity of the beam rastering on the solid lithium target.

The first commercial NBS system from this partnership underwent testing at BINP before beginning installation at its permanent location. First operations of the NBS have proved the architecture concept. At present, the system is in its final commissioning stage with operational parameters meeting or exceeding the design specifications.

O109

A neutronic design for an epithermal BNCT beam at an MTR-type research reactor

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Egypt Second Research Reactor (ETRR-2) is a Material Testing Reactor (MTR) with a nominal power of 22 MW. The reactor is in operation since 1998. Boron Neutron Capture Therapy (BNCT) beam had been planned from the design stage of the ETRR-2. However, this beam has not yet been utilized. Many modifications are needed to achieve the in-air parameters recommended by the International Atomic Energy Authority (IAEA). Design problems in the current thermal column beam have been analyzed by the authors before. The modifications needed to develop a thermal BNCT beam for research and liver treatment purposes were analyzed.

In the light of the need for optimum utilization for epithermal BNCT applications, the needed design modifications for the thermal column beam have been investigated in this work. A previously developed and validated Monte Carlo N-Particle (MCNP) model for the ETRR-2 reactor has been used. The MCNP code is also used in this work to perform the neutronic design of the beam. A new design method for a multi-layered spectrum shifter; which was recently developed by the authors; was applied to improve the design process of the epithermal beam. The design method is based on two concepts: stepwise spectrum shifting and separation of the design process into two design stages, namely the material selection and the thickness determination.

The in-air parameters for the proposed epithermal BNCT beam for the ETRR-2 are calculated. The results show that the beam could be very efficient for epithermal BNCT research purposes. Moreover, considering the epithermal BNCT beam for clinical treatment purposes, it has been found to be comparable to Petten BNCT beam.

Keywords:
BNCT, Epithermal neutron beam design, MTR-type research reactor, MCNP.

Design improvements of thermal boron neutron capture therapy beam at an MTR-type research reactor

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Egypt Second Research Reactor (ETRR-2) is a Material Testing Reactor (MTR) with a nominal power of 22 MW. The reactor is in operation since 1998. As it is a Multi-Purpose Reactor, the design concept of ETRR-2 is based on the requirement of being a reactor of versatile utilization. Considering the optimum utilization of the thermal column beam at Egypt second research reactor (ETRR-2) for Boron Neutron Capture Therapy (BNCT), the development of the thermal BNCT beam has been investigated.

Monte Carlo N-Particle (MCNP) code has been used for neutronic calculations. A previously developed and validated MCNP model for ETRR-2 reactor has been used as a starting point for the design work. However, various modifications have been done in this model to focus on the thermal column as well as to simulate and develop the proposed thermal beam designs. Also, the experimental measurements; performed to validate the model; are presented and compared with previous measurements. In the experiment, the triple bare flux monitors method has been used.

Design problems in the current beam have been analysed. The modifications needed to develop thermal BNCT beam for research and liver cancer treatment purposes are presented. The in-air beam parameters are calculated. The results show that the beam could be efficient for research purposes.

Keywords:
BNCT, thermal neutron beam design, MTR-type research reactor, MCNP.

O142

BNCT Neutron Beams should be evaluated by Combining Physical, Radiobiological, and Dosimetric Figures of Merit.

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Since it was published in 2001, the IAEA TecDoc-1223 recommendations on beam quality are used as a reference for the evaluation of BNCT Beam Shaping Assemblies (BSA). These figures of merit assess the quality of a neutron beam by its physical characteristics evaluated in air. Even though these figures of merit are very useful to establish the essential neutron beam characteristics for BNCT, they are not adequate to predict the clinical performance of a proposed BSA. To this purpose, other parameters were proposed, such as: advantage depth, advantage depth dose rate and advantage ratio. Nevertheless, these parameters do not take into account the tridimensional dose distribution in a clinical target.

We are presenting a method to assess the therapeutic potential and the safety of a neutron beam designed for clinical application, employing radiobiological and dosimetric figures of merit.

We propose the use of Tumor Control Probability (TCP), Normal Tissue Complication Probability (NTCP) and Uncomplicated Tumor Control Probability (UTCP) calculated from three-dimensional in-phantom dose distributions. Combined with in-patient out-of-beam dosimetry, we show that these criterions can be used to assess the quality and safety of a neutron beam.

This approach highlights that free-beam, in-air parameters may exclude a designed beam that can still ensure an advantageous dose distribution in patients [1]. It is thus important to enlarge the field of view when evaluating the feasibility of BNCT with a neutron beam designed for a clinical facility. Moreover, the proposed figures can assess the therapeutic potential of different beams on real clinical scenarios [2]. This means that beams can be compare overall by using a single scalar variable (i.e., UTCP).

In this respect radiobiological data are essential to feed models for a correct dosimetry and for the calculation of proper figures of merit. In this work, Head and Neck cancer data are used for UTCP computation. Anyhow, there is a general lack of data for healthy tissues, which is needed to build Normal Tissue Complication Probability (NTCP) models. In this presentation, the INFN project IT_STARTS, aimed at including more radiobiological models into the treatment planning, will be described.

Keywords:
BNCT; BSA; UTCP; epithermal neutron beam; radiobiological figure of merit; out- of-beam dosimetry

References:

[1] Postuma I., et al. A Novel Approach to Design and Evaluate BNCT Neutron Beams Combining Physical, Radiobiological, and Dosimetric Figures of Merit. Biology 2021, 10,
174. https://doi.org/10.3390/biology1003017
[2] Provenzano L, et al. The essential role of radiobiological figures of merit for the assessment and comparison of beam performances in boron neutron capture therapy. Physica Medica. 2019 Nov 1;67:9-19. https://doi.org/10.1016/j.ejmp.2019.09.235

O148

Review of the different AB-BNCT facilities worldwide according to the ALARA criterium.

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Presently, there are a number of different facilities worldwide, some already working and some under construction, for Accelerator-Based BNCT (AB-BNCT) ranging 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 electrostatic quadrupole (working on ^{9}Be(d,n) or ^{13}C(d,n) at 1.5 MeV).

In this presentation we will discuss these installations from the point of view of activation, both at the target and also at the facility level. Since these facilities are intended to work in hospital environments one of the guiding criteria should be the ALARA (As Low As Reasonably Achievable) one.

A thorough analysis will be made evaluating the residual radioactivity produced both by the primary nuclear reaction at the target and beam line, and also by the generated neutrons in the surrounding areas like Beam Shaping Assembly, shielding materials and patient treatment room.

Keywords:
AB-BNCT, Nuclear Reactions. Induced Radioactivity. ALARA.

Gamma-ray contributions induced by $^{7}Li(p, \gamma)^{8}Be$ and $^{7}Li(p, p')^{7}Li$ reactions in the Li-based AB-BNCT

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Gamma-ray production in a ^{7}Li target bombarded by relatively low energy (< 3 MeV) protons is known attributed mainly from the $^{7}Li(p,p')^{7}Li$ reaction as discussed by Lee et al., and this was how most studies in Li-based AB-BNCT design considered. However, the reaction channel, $^{7}Li(p, \gamma)^{8}Be$, was absent, which could contribute also to the gamma-ray production. Although the total yield is much lower comparing to the (p, p') reaction, the radioactive capture reaction results in two much more energetic gamma rays (> 14 MeV), which is considerable in dose calculation. This study shows notable dose contributions to the total background dose from the (p, p') and (p, γ) reactions, especially when a near-threshold scene was considered (thin moderator without additional gamma-ray shielding); such an influence is much insignificant when a 2.5-MeV proton energy was used and a thick moderator is applied; the thick moderator provides a certain level of self-shielding. The gamma-ray contribution to the normal tissue dose is high in the near-threshold case, and the portion attributed from radioactive capture reaction cannot be ignored. From this study, it is suggested that a carefully controlled thickness of Li active layer is necessary; a thick Li layer (thicker than the range of delta energy between initial energy and the threshold energy, i.e. 1.88 MeV) results in more (p, p') and (p, γ) reactions but no additional neutron produced. Furthermore, a slightly thinner Li-7 active layer thickness may benefit the beam quality in a 2.5-MeV proton driven AB-BNCT.

Keywords:
$^{7}Li(p,p')^{7}Li$ and $^{7}Li(p, \gamma)^{8}Be$ reaction, Gamma-ray contributions, Li-based AB-BNCT

O75

An Explorative Study of Advantage Depth over Neutron Beam Energy, Spatial, and Angular Distributions in BNCT

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Introduction: One of the limiting factors in BNCT application is the treatable depth for deep-seated tumor, and therefore the advantage depth (AD) has become an important research topic in neutron beam design. On the Physics Working Group Meeting in 2016 during the ICNCT-17, our group has presented an energy dependent AD, and pointed out a different optimal energy, saying around 6 keV, than the conventional one, i.e., 10 keV. Further to the energy dependence, we have focused on the domains of spatial and angular distributions. This work has identified several meaningful parameters affecting AD and provide a new insight into the neutron beam design.

Materials and Methods: AD performance was investigated for monoenergetic neutron beam irradiation of a Snyder head phantom through MCNP6 simulation. The Snyder head phantom has been processed into a voxel-based model. To evaluate the energy-spatial distribution influence, the neutron beam was set as a disk source with two separate parts – one inner disk and an outer ring area which have different neutron energies. Non-uniform neutron energy distribution can be simulated by setting different neutron energies in the two areas. Several parameters of neutron beam and tumor/normal tissue (T/N) ratio were varied to study their influence on AD.

Results: When the beam was incident along the longitudinal axis of the Snyder phantom, we found that a non-uniform neutron energy distribution has better AD performance. The maximum AD is obtained when the energy of the outer ring is slightly higher. The best energy combination changes according to the T/N ratio, and a slightly higher energy of the outer ring still delivers better outcome. In the case of neutron beam with different angular distributions, AD decreases as the beam becomes more divergent. Meanwhile, the more divergent the neutron beam, the larger is the desired energy difference between the outer ring and the inner disk.

Conclusion: Comparing with the uniform energy distribution, a higher energy of neutrons emerging from the outer ring ensures a better AD, showing the effect of a non-homogeneous energy distribution. Several parameters have an influence on the best energy combination, such as the angular distribution of neutron beam and T/N ratio. Further details will be presented in our completed report and presentation.

Keywords:
BNCT beam design, advantage depth, non-uniform energy distribution, dose performance

Topology optimization of a BNCT neutron moderator

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To slow down neutrons to the energies commonly accepted to limit the side effects of a Boron Neutron Capture Therapy (BNCT), i.e. En < 10 keV, and to optimize their capture rates on the ^{10}B fixed in tumors, moderators placed between the patients and the neutron source are to be considered. These moderators, the use of which is essential with the shift in favor of accelerator- based sources, are usually made of a sandwich of low atomic mass materials, the composition and thickness of which being adjusted according to the level of hardness of the energy spectrum of the neutrons desired. Their current design is parametric. First, an intuitive sample of materials and characteristic dimensions is built, based on literature and/or experience feedback. Then, for each possible configuration of moderator, a Monte-Carlo calculation is performed to simulate the transport of particles within it and to compute the doses deposited during the BNCT. Finally, the moderator offering the best compromise between therapeutic and economic objectives is chosen. These parametric design steps are now sufficient to guarantee a dose deposition of 30 Gy-Eq in a tumor with an average dose in healthy tissues relatively under control. However, they cannot prevent the deposition of high doses, of hot spot type, in a fraction of healthy tissues upstream of the tumor, e.g. in the scalp during the treatment of glioblastoma, with adverse consequences documented in the literature. To reduce the total doses deposited in healthy tissues, we propose to use a topology optimization algorithm recently developed at the LPSC, capable of autonomously computing the optimal composition and shape of any neutron moderator coupled with any neutron source. In this communication, we will present an example of optimization of a specific AB-BNCT configuration, consisting of a heavy water moderator embedded in a concrete wall, coupled to a $^{9}Be(d(1.45MeV),n)$ neutron source, whose energy and angle distribution has been measured and integrated into the Monte-Carlo simulations. The algorithm succeeds in finding shapes of D2O moderators that avoid deposition of doses exceeding recommended limits in 95% of a patient's head in the case of a medium-depth glioblastoma treatment. In the remaining 5%, the doses deposited do not exceed the limits by more than a few percent. We will additionally show how the optimal shape and performances of a moderator evolve with the depth of the tumor to be treated. The moderators computed have complex shapes, inaccessible in their details to human intuition and parametric design.

O117

Application of high fidelity radiation transport models to facility design, material selection, and shielding concepts for p-7Li accelerator based BNCT

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The Alphabeam system, a turnkey clinical solution for boron neutron capture therapy (BNCT) developed by TAE Life Sciences, includes a compact tandem accelerator, robotic couch, treatment planning system and lithium targets. The start of installation for the first Alphabeam system at the CNAO center in Pavia, Italy is expected by 2023. Protons are accelerated up to 2.5 MeV onto a 100 micron thick natural lithium target, where neutrons are produced via the ^{7}Li(p,n)^{7}Be and ^{7}Li(p,n)^{7}Be* nuclear reactions. The expected anisotropic neutron yield, derived from first principles, is 9.9E11 neutrons per second per mA. Uncertainties in differential reaction cross sections and proton stopping powers in lithium metal lead to upper and lower bounds for the angular distributions and energy spectra of these neutrons. These calculations are consistent with published thick target yields.

The target neutrons are moderated to obtain a clinically-acceptable treatment beam meeting IAEA guidelines [1]. Both treatment beam neutrons and those scattered out of it impact the facility design, as well as radiation protection planning due to undesirable activation of Alphabeam and facility components. Additional dose contributions from multiple photon sources are significant. A key source of photons are proton reactions in the lithium target, namely 478 keV photons from the ^{7}Li(p,p')^{7}Li* inelastic scattering reaction and photons with energy > 14.6 MeV from the subsequent decay of the ^{8}Be nucleus produced in the ^{7}Li(p,gamma)^{8}Be* reaction. High fidelity, time-dependent, radiative transport models were developed in MCNP6 to understand the potential radioactive hazards associated with each of these source terms on timescales that spanned a single treatment interval through the end-of-life for the facility. These results are consistent with similar calculations performed by CNAO researchers using the FLUKA Monte Carlo code. Details will be presented on the impact of the expected neutron spectrum on facility layout decisions, limitations on structural materials, and the allowable quantities of elements used in ancillary components throughout. In addition, results will show the shielding design of the facility is driven by the high energy photons produced within the lithium target.

Keywords:
Monte Carlo, Neutron Sources, Accelerators, Activation, Dosimetry, Shielding

References:

[1] International Atomic Energy Agency, "Current status of neutron capture therapy," IAEA-TECDOC-1223 (May 2001).

Research on depositing a thin coating on the lithium neutron production target by magnetron sputtering technology

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Accelerator-based neutron sources (ABNS) is being researched to supply neutrons for boron neutron capture therapy (BNCT) [1-7]. Lithium is a promising target material to generate relatively-low energy neutron by $^{7}Li(p,n)^{7}Be$ reaction [8-10]. But lithium target still faces following problems: easily reacts with air to form compounds, lithium evaporation and so on [11,12]. X.-L. ZHOU et al. has studied the substitution of pure lithium with lithium compounds, and found that neutron yields decreases distinctly [13]. To tackle lithium evaporation, S. Ishiyama et al. synthesized lithium nitride on the surface of lithium target by in-situ nitridation techniques, due to its thermal stability of up to 1,086 K [14,15]. Yoshiaki Kiyanagi et al. attached a thin metal plate to the target by hot isostatic pressing to make a sealed lithium target [3].

To protect lithium from air, we considered depositing a thin anticorrosion coating on the lithium target. Such a lithium target could avoid compounds formation and lithium evaporation. A thin coating could decrease the neutron yield as little as possible. The physical vapor deposition (PVD) is proved to be a simple, low-cost and green technology that has been widely utilized to put protective films on metals and alloys [16,17]. PVD includes magnetron sputtering, vacuum evaporation, ion plating, etc. The magnetron sputtering was selected in this study for its advantages of high speed, outstanding adhesion, easy control of film thickness, and good film formation property [18,19]. Besides, its' low deposition temperature ensures that lithium will not melt during the coating process. As for the coating material, aluminum [20], chromium [21] and titanium [22,23] were selected for their good thermal stability and excellent corrosion resistance.

In this work, the aluminum, chromium and titanium coating was analyzed and compared theoretically from their physical properties, nuclear reactions with protons and neutrons. The Monte Carlo simulations were made to estimate the effects of the coating on incident protons and neutron yield. A coating of different material with same thickness was deposited on the lithium target by magnetron sputtering technology. The color change process of coated and bare lithium samples in the air were observed and compared to infer the lithium chemical state qualitatively. The chemical elements, compositions and surface morphology of the samples were characterized by XPS, EDS, SEM measurements. The components of samples after being exposed in the air were inferred by their XRD patterns. It was found that the influence of a thin metal coating of hundreds nanometers on the incident protons and neutron yield could be ignored. Depositing an aluminum, chromium or titanium coating on the lithium target by magnetron sputtering technology is feasible. Such a coating is effective to prevent lithium from deteriorating reaction with air to form compounds. Among these three materials, aluminum coating has the smallest side effects, but titanium coating has the best performance of lithium protection. A uniform titanium coating with a thickness of 200-nm could effectively isolate lithium from air and stabilize its chemical state for at least 9 hours, at a relative humidity of 50% and a temperature of 25ºC. The lithium target with a thin coating is more convenient to storage and transport than a bare lithium target, and it could be directly installed and replaced on the accelerator beam line in the air, with no need to be performed in a vacuum or an ultra-low humidity environment.

Keywords:
BNCT; lithium target; lithium anticorrosion; coating

References:

[1] Shefer, R.E.; Klinkowstein, R.E. Accelerator-based epithermal neutron beam design for neutron capture therapy. Med. Phys. 1992, 19, 709–721, doi:10.1118/1.596815.
[2] T.E., B.; J.C., Y. Accelerator-based epithermal neutron sources for boron neutron capture therapy of brain tumors. J. Neurooncol. 2003, 62, 19–31, doi:10.1023/A:1023247222043.
[3] Yoshioka, M. Review of Accelerator-Based Boron Neutron Capture Therapy machines. 2016, 5–9.
[4] Fantidis, J.G. Beam shaping assembly study for BNCT facility based on a 2.5 MeV proton accelerator on Li target. J. Theor. Appl. Phys. 2018, 12, 249–256, doi:10.1007/s40094-018-0312-1.
[5] Kiyanagi, Y. accelerator-based neutron source for boron neutron capture therapy. Ther. Radiol. Oncol. 2018, 769, doi:10.1088/1742-6596/769/1/012064.
[6] Taskaev, S.; Kasatov, D.; Makarov, A.; Ostrenov, Y.; Shchudlo, I.; Sorokin, I.; Bykov, T.; Kolesnikov, I.; Koshkarev, A.; Sokolova, E. Accelerator neutron source for Boron Neutron Capture Therapy. IPAC 2018 ninth Int. Part. Accel. Conf. 2018, 550–552, doi:10.18429/JACoW-IPAC2018-MOPML062.
[7] Suzuki, M. Boron neutron capture therapy (BNCT): a unique role in radiotherapy with a view to entering the accelerator-based BNCT era. Int. J. Clin. Oncol. 2019, 1–8, doi:10.1007/s10147-019-01480-4.
[8] Lee, C.L.; Zhou, X.-L. An algorithm for computing thick target differential p-Li neutron yields near threshold. In Proceedings of the AIP Conference Proceedings; AIP, 1999; Vol. 227, pp. 227–230.
[9] Lee, C.L.; Zhou, X.L. Thick target neutron yields for the 7Li(p,n)7Be reaction near threshold. Nucl. Instruments Methods Phys. Res. Sect. B Beam Interact. with Mater. Atoms 1999, 152, 1–11, doi:10.1016/S0168-583X(99)00026-9.
[10] Pachuau, R.; Lalremruata, B.; Otuka, N.; Hlondo, L.R.; Punte, L.R.M.; Thanga, H.H. Thick and thin target 7Li(p,n)7Be neutron spectra below the three-body breakup reaction threshold. Nucl. Sci. Eng. 2017, 187, 70–80, doi:10.1080/00295639.2017.1291053.
[11] Bayanov, B.; Belov, V.; Kindyuk, V.; Oparin, E.; Taskaev, S. Lithium neutron producing target for BINP accelerator-based neutron source. 2004, 61, 817–821, doi:10.1016/j.apradiso.2004.05.032.
[12] Matysiak, W.; Prestwich, W. V.; Byun, S.H. Precise measurements of the thick target neutron yields of the 7Li(p,n) reaction. Nucl. Instruments Methods Phys. Res. Sect. A Accel. Spectrometers, Detect. Assoc. Equip. 2011, 643, 47–52, doi:10.1016/j.nima.2011.04.034.
[13] Zhou, X.L.; Lee, C. Lithium compounds as targets for (p,n) reactions. Appl. Radiat. Isot. 1997, 48, 1493–1496, doi:10.1016/S0969-8043(97)00145-0.
[14] Ishiyama, S.; Baba, Y.; Fujii, R.; Nakamura, M.; Imahori, Y. synthesis of lithium nitride for neutron production target of BNCT by in-situ lithium deposition and ion implantation. Nippon Kinzoku Gakkaishi/Journal Japan Inst. Met. 2013, 77, 497–502, doi:10.2320/jinstmet.J2013048.
[15] Ishiyama, S.; Baba, Y.; Fujii, R.; Nakamura, M.; Imahori, Y. Direct Synthesis of Li3N Thin Layer on Lithium Target Surface for BNCT in N2 Gaseous Conditions. Mater. Trans. 2013, 54, 1765–1769, doi:10.2320/matertrans.M2013212.
[16] Henini, M. Handbook of Thin-Film Deposition Processes and Techniques. Microelectronics J. 2000, 31, doi:10.1016/s0026-2692(99)00122-6.
[17] Frey, H.; Khan, H.R. Handbook of Thin-Film Technology; 2015;
[18] Musil, J. Recent advances in magnetron sputtering technology. Surf. Coatings Technol. 1998, 100–101, doi:10.1016/S0257-8972(97)00633-6.
[19] Tan, X.Q.; Liu, J.Y.; Niu, J.R.; Liu, J.Y.; Tian, J.Y. Recent progress in magnetron sputtering technology used on fabrics. Materials (Basel). 2018, 11, doi:10.3390/ma11101953.
[20] B.D.R. Aluminum coating for the corrosion protection of welds 2006.
[21] Lin, N.; Xie, F.; Zhou, J.; Wu, X.; Tian, W. Corrosion behaviors of P110 steel and chromium coating in CO 2-saturated simulated oilfield brine. J. Wuhan Univ. Technol. Mater. Sci. Ed. 2011, 26, doi:10.1007/s11595-011-0195-3.
[22] Jeyachandran, Y.L.; Karunagaran, B.; Narayandass, S.K.; Mangalaraj, D.; Jenkins, T.E.; Martin, P.J. Properties of titanium thin films deposited by dc magnetron sputtering. Mater. Sci. Eng. A 2006, 431, 277–284, doi:10.1016/j.msea.2006.06.020.
[23] Shyjumon, I.; Gopinadhan, M.; Helm, C.A.; Smirnov, B.M.; Hippler, R. Deposition of titanium/titanium oxide clusters produced by magnetron sputtering. Thin Solid Films 2006, 500, 41–51, doi:10.1016/j.tsf.2005.11.006.

Optimization of a beam-shape assembly based on proton accelerator for Boron Neutron Capture Therapy

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Boron Neutron Capture Therapy (BNCT) is being promoted with the development of accelerator neutron sources, and many new accelerator-based facilities are being built. A-BNCT facilities can be placed in hospitals with high safety and low construction and maintenance costs. The therapeutic effect of BNCT mainly depends on the quality of the epithermal neutron beam, and the beam-shape assembly has a great influence on the beam quality. In this paper, we present a beam-shape assembly for 7MeV proton accelerator, using alloy moderator materials composed of five elements: Mg, Al, F, O, and Li. The calculation results show that the epithermal neutron beam energy is up to , the fast neutron component and the gamma ray component under free-air condition are both lower than , in line with IAEA design requirements.

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Design of a filtration system to improve the dose distribution for an accelerator-based BNCT

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Purpose: The aim of this study is to conduct a Monte Carlo simulation to design and evaluate a neutron filtration system to improve the dose distribution of an accelerator-based neutron capture therapy system and introduce the concept of intensity modulated boron neutron capture therapy.

Methods: The Particle and Heavy Ion Transport code System (PHITS) was used in this study. A LiF ceramic composed of 99% enriched ^{6}Li was utilised to filter out low energy neutrons to increase the average neutron energy. Three different filter designs were modelled and the thermal neutron flux and the biologically equivalent dose distribution inside a water phantom was simulated. The accelerator is operating with a proton beam current of 1 mA, with the capacity to operate at 2 mA. Therefore, the loss of neutron intensity by inserting a filter can be compensated by increasing the proton current. A filter shape and thickness that reduced the peak thermal neutron intensity by half, while maintaining a high thermal neutron flux at a deep region was investigated. After an appropriate filter shape and thickness was evaluated for each design, a simulation of a BNCT treatment of the brain was performed using a humanoid head phantom and the dose distribution in a mock tumour located 4 cm and 8 cm depth along the central beam axis was evaluated. A dose limit of 15 Gy-eq to the brain was set.

Subsequently, a simulation of a BNCT treatment of the head and neck was performed using the same phantom. A polyethylene loaded with natural LiF was modelled in addition to the ^{6}Li filter to partially block the neutron beam to shield the dose limiting organ (mucosa membrane). The dose distribution in a mock tumour and mucosa membrane was simulated with and without the shield. A dose limit of 12 Gy-eq to the mucosa membrane was set.

Results: All three filters improved the beam penetration of the accelerator-based neutron source. Filter design C was found to be the most suitable filter, having an advantage depth of 10.4 cm with a treatment time of 44.7 minutes. Compared with the unfiltered beam, the mean absorbed dose in a tumour located at a depth of 8 cm was increased by approximately 40%. For the head and neck simulation, the combination of polyethylene loaded with natural LiF and filter design C decreased the dose to the mucosa membrane by approximately 20%, effectively increasing the dose delivered to the tumour by approximately 20%.

Conclusion: A neutron filtration system for an accelerator-based BNCT system was investigated using Monte Carlo simulation. The proposed filter design significantly improved the dose distribution for both brain and head and neck BNCT. Future work will involve manufacturing of the filter to perform experimental validation and the end goal is to apply this filter in the clinic for patients receiving BNCT.

Keywords:
Boron neutron capture therapy, Thermal neutrons, Neutron moderator, Monte Carlo simulation

Feasibility study on optimization of beam shaping assembly for accelerator-based neutron source for BNCT using deterministic particle transport calculation code

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1. Background

In recent accelerator-based BNCT, it is necessary to moderate the fast neutrons to epithermal neutron region using a Beam Shaping Assembly (BSA). The BSA is composed of a moderator, a reflector, a collimator, filters, etc. The materials and thickness of each component must be optimized to satisfy the neutron beam parameters for BNCT specified by the IAEA guideline TECDOC-1223. In the conventional BSA optimization, the BSA is constructed after individual component optimization.[1] However, such individual optimization cannot consider the interaction between components in the optimization stage. As a result, the IAEA standards may not be satisfied. In addition, when the Monte Carlo method is used for the optimization calculation, it requires a huge amount of calculation time, which may prevent effective optimization from being performed in a realistic time. Therefore, in this study, we adopt a deterministic neutron-transport calculation method to accomplish optimizing BSA simultaneously.

2. Materials and Methods

The optimization of BSA was carried out by referring to the neutron irradiation field being studied in the iBNCT project at the University of Tsukuba.[2] This study aimed to obtain higher quality neutrons than the conventional BSA by optimizing each component of the BSA as two layers in a two-layer BSA. [3]

As a method to optimize each component of the BSA simultaneously, we adopted a genetic algorithm (GA) [4] that searches for the optimal solution by imitating the process of biological evolution. In this method, an objective function (fitness function) using the neutron beam parameters for BNCT specified by IAEA was set as an optimization index. For the neutron transport calculation, the deterministic particle transport calculation and general-purpose reactor physics code system CBZ[5] was adopted to reduce the calculation time.

3. Results and Discussion

As a result of the BSA optimization by the genetic algorithm using the CBZ code under the condition that the optimization calculation is performed only for 100 generations with 30 individuals per generation, the following material combination was found to be the best solution: the moderator using Fe + AlF_3, the reflector using ^{60}Ni + Pb, the collimator using PbF_2 + Poly-B, the thermal neutron filter using LiF, the fast neutron filter using Fe, and the γ-ray filter using ^{60}Ni. The combination of these components in the BSA fully satisfied the IAEA standards.

For the comparison of computing time, GA optimization using CBZ code took only 50 – 100 seconds per individual, on the contrary, the Monte Carlo particle transport code, PHITS, took 26 – 40 hours. By using CBZ code, the calculation time was significantly reduced.

4. Conclusions

The optimization method used in this study will enable the simultaneous optimization of each component of the BSA and will significantly reduce the calculation time compared to Monte-Carlo based optimization.

Keywords:
Optimization, Beam Shaping Assembly, Genetic Algorithm, IAEA

References:

[1] Jacob G. Fantidis et.al, "Optimization of Beam Shaping Assembly design for Boron Neutron Capture Therapy based on a transportable proton accelerator" Alexandria Engineering Journal 57, 2333–2342 (2018)
[2] Hiroaki Kumada et. al, "Development of beryllium-based neutron target system with three-layer structure for accelerator-based neutron source for boron neutron capture therapy" Applied Radiation and Isotopes 106 p.78–83 (2015)
[3] Bilalodin et.al, "Optimization of double layered beam shaping assembly using genetic algorithm" The Journal of Polish Society of Medical Physics Vol 24, Issue 4 (2018)
[4] Mehmet Türkmen et.al, "A new method in beam shaping: Multi-Objective Genetic Algorithm method coupled with a Monte-Carlo based reactor physics code" Progress in Nuclear Energy 99 p.165-176 (2017)
[5] G.Chiba, T.Endo, "Numerical benchmark problem of solid-moderated enriched-uranium-loaded core at Kyoto University Critical Assembly," J. Nucl. Sci. Technol., 57, p.187-195 (2020).

The design and optimization of BSA and Irradiation room for $^{7}Li(p,n)^{7}Be$ in AB- BNCT

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Introduction

BNCT is a tumor selective treatment that after injection of tumor localizing drug which contains Boron, tumor is bombarded with epithermal neutrons. Epithermal neutrons are slowed down through the matter to become thermal neutron at the tumor position. Then Boron interacts with thermal neutron and alpha is produced to kill the cancer cells. Accelerator-Based (AB-BNCT) are neutron sources for clinical environments which are good alternatives of reactors. The $^{7}Li(p,n)^{7}Be$ is one of the reactions that is used as the neutron producing. The primary neutron beam needs a Beam Shaping Assembly to increase the flux of epithermal neutron and remove contamination of beam. The aim of this project is optimize and design of the BSA with the use of MCNPX code to produce a high flux of epithermal neutron to decrease the time of treatment and reduction of radiation damage.

Procedure and Methodology

In this work, the 2MeV proton beam has reacted with 2μm Lithium target. Moderator has been modeled as cylindrical shape which different groups of candidates (Al-Li_2Co_3-Teflon, CaF_2- AlF_3-Teflon, MgF_2-AlF_3) have been sandwiched in order in different thicknesses(The thickness has been varied between 1cm and 1.5cm and both of 1cm and 1.5cm) and all of the BSA has been surrounded by reflector (Lead and Pb).

Result

Among different candidate, the combination of MgF_2 and AlF3 with each layer 1.5cm (with 60cm total thicknesses) with Lead as a reflector have the best parameters according to IAEA recommendation. There are a layer of Bismuth and ^{6}Li at the end of BSA to decrease the gamma and thermal neutron contamination. In order to have an optimal treatment, it is important to decrease the fast and thermal neutron of beam in treatment room (1). Therefore, there are 20m of Poly-Li walls to observe contamination and reduce the side-effects. Figure 1 has shown the shape of BSA and the distribution of fast neutron in poly-Li walls of treatment room.

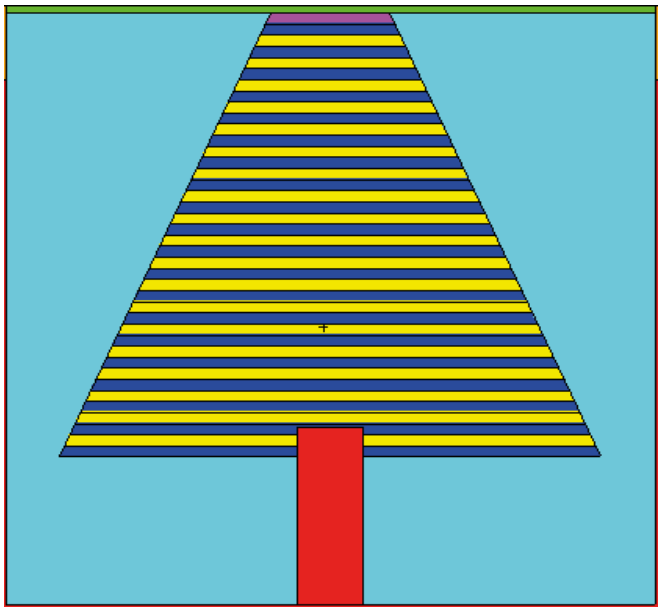
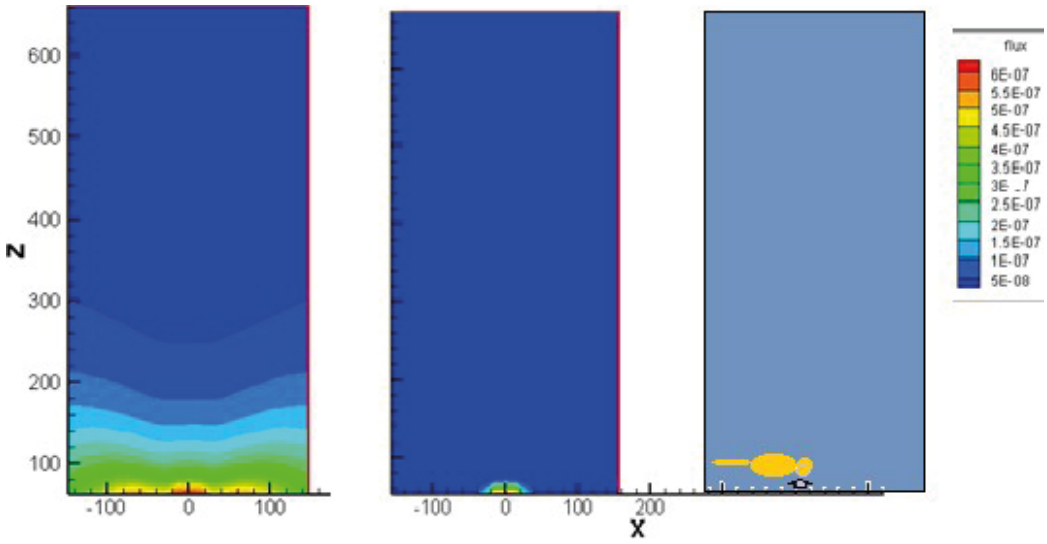


Figure 1: a) the geometry of BSA

b) The distribution of fast neutron with and without poly-li walls and schematic picture of treatment room



Keywords:
BNCT,^{7}Li(p,n)^{7}Be, BSA, Irradiation room

References:

[1] Magni, Chiara, Ian Postuma, Michele Ferrarini, Nicoletta Protti, Setareh Fatemi, Chunhui Gong, Umberto Anselmi-Tamburini et al. «Design of a BNCT irradiation room based on proton accelerator and beryllium target.» *Applied Radiation and Isotopes* 165 (2020): 109314.

Alliflu: a novel material for the Beam Shaping Assembly of an AB-BNCT clinical facility

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This work is performed in the context of the design of a clinical neutron beam produced with the INFN proton RFQ accelerator coupled to a beryllium target. A Beam Shaping Assembly (BSA) whose main constituent is lithiated aluminum fluoride has been designed for the treatment of deep-seated tumours [1].

Aluminum fluoride (AlF3) is commercially available only in the form of powder, not adequate to build a compact BSA with uniform and stable density and proper mechanical characteristics. A fully dense material can be obtained through a sintering process, that, for this compound, is complicated by a significant high-temperature volatility. To overcome this problem, a fast, pressure assisted, sintering procedure must be used. A custom Field Assisted Sintering (FAST) apparatus was designed and prototyped for this purpose at the mechanical workshop of INFN Pavia (Italy), and the obtained material was named *Alliflu*. Due to the low solubility of Li in AlF_3 the densified material contains a mixture of AlF_3 and Li_3AlF_6. The microstructure of the material deriving from different sintering and mixing procedures has been characterized by Scanning Electron Microscope (SEM) analysis and optimized in order to achieve a good uniformity in the Li distribution.

Since the densified lithiated aluminum fluoride is a new material, several characterizations are needed in view of its use in the BSA. This work illustrates the experimental and computational studies that were conducted to this end.

First, a Neutron Activation Analysis study was performed by irradiating AlF3 samples in the research nuclear reactor of Pavia, to quantify the trace elements present in the material. The measured composition was implemented in a Monte Carlo model of the clinical facility, and simulations of clinical irradiations were run to comprehensively evaluate the neutron activation of the BSA due to a BNCT treatment. To reduce the dose component resulting from the BSA induced radioactivity, a shielding in the patient area is being studied testing different configurations.

The mechanical resistance of the new material was studied by means of compression tests on *Alliflu* samples with different values of densities, ranging from about 70 to 99% of the theoretical one. Moreover, samples with identical density were exposed in the Pavia reactor to a neutron fluence comparable to about one thousand clinical irradiations. The goal is to investigate the possible effects of neutron irradiation on the capacity of the material to sustain compression, compared to the resistance of the material before irradiation. Preliminary tests

showed a different behavior of the irradiated samples with respect to the non-irradiated ones. New compression tests are planned with a more effective testing machine and a larger number of samples, to better highlight the dependence of the mechanical resistance of the material on the density and on the neutron dose.

Finally, the moderation properties were studied by neutron transmission experiments at the INFN Legnaro National Laboratories: *Alliflu* bricks were irradiated with neutrons produced by the 5 MeV proton beam of the CN proton accelerator coupled to a beryllium target, having the same spectral characteristics as the neutron beam of the RFQ. Monte Carlo simulations of the neutron interaction with *Alliflu* were validated with the experimental spectra obtained with two different detectors.

The presented studies aim at producing useful results for the implementation of RFQ- based BNCT, with a comprehensive evaluation of a new material as relevant component of the clinical facility.

Keywords

accelerator-based BNCT, Beam Shaping Assembly, radiation protection, neutron activation, dosimetry

References:

[1] I. Postuma et al., A Novel Approach to Design and Evaluate BNCT Neutron Beams Combining Physical, Radiobiological, and Dosimetric Figures of Merit. Biology, 2021, 10, 174

Optimized beam shaping assembly for a 2.1-MeV proton-accelerator-based neutron source for boron neutron capture therapy

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Boron Neutron Capture Therapy (BNCT) is facing a new era where different projects based on accelerators instead of reactors are under development. In order to improve the therapeutic effect of BNCT, a well defined and optimized epithermal neutron spectrum is fundamental. To this aim, the possibility of designing a beam shaping assembly (BSA) specially suited for low energy accelerators is key. An optimized BSA for BNCT was designed based upon the proton on lithium reaction at specially low energy was pursued [1]. The beam obtained with the designed BSA accomplishes all the IAEA recommendations for proton energies between 2.0 and 2.1 MeV. The beam profits from a high energy tail that is particularly short due to the neutron production kinematics, where the highest energy neutrons produced at the target do not surpass 350 keV. In addition, the neutron beam is well moderated so that the neutron spectrum peaks at 2 keV. This underlies the design of the neutron beam, where less than one third of the fast neutron flux corresponds to neutrons above 40 keV. This is further supported with dose estimations in standard phantoms as an ICRU33 tissue cylinder and the Snyder phantom, which confirm the adequacy of the beam for BNCT. Besides, there is an overall improvement of the figures of merit with respect to BNCT facilities and previous proposals of new accelerator-based facilities.

Keywords:

BSA design, lithium target, IAEA recommendations, low energy accelerator

References:

[1] Torres-Sánchez, P., Porras, I., Ramos-Chernenko, N. *et al.* Optimized beam shaping assembly for a 2.1-MeV proton-accelerator-based neutron source for boron neutron capture therapy. *Sci Rep* **11,** 7576 (2021). https://doi.org/10.1038/s41598-021-87305-9

Features of bsa design and basic concept of radiation room for NCT studies at the IRT-t research reactor

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According to published statistics at the end of 2018 more than 1.3 million people had affected by different types of tumors in Russian Federation and the number of new registered cases still continue to increase. Currently in Russia there are no approved radiation facilities for NCT cancers treatment so this paper devoted to BSA design at research reactor tangent channel and design of medical irradiation room to conduct safe NCT studies at the IRT-T research reactor. As the way of improvement of initial neutron beam parameters the following constructions were applied: incore graphite reflector and in-shutter filters made of Bi, Pb, and Al. As result neutron and gamma doses is reduced at 2 and 7 times, respectively. Based on permissible dose rate value (2.7 nSv/s) in Russian Federation the dosimetric calculations of radiation room walls made of shielding materials were conducted.

Product and Facility Design Optimization for an Accelerator BNCT Building Expansion Project in Pavia, Italy

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Worldwide, relatively few accelerator-based BNCT facilities have been successfully completed and are in clinical operation. TAE Life Sciences, CNAO, and Studio Calvi have partnered to incorporate the Alphabeam BNCT system into the design of a two-treatment room suite within a larger facility expansion project for CNAO. Start of construction for the multiyear project in Pavia, Italy is planned for late 2021 and operation of the BNCT system integrated with existing hadrontherapy modalities is expected by 2024.

This project balances Alphabeam system requirements with the inherent space constraints and logistical challenges of a "building expansion" type of project. Key elements of the design include the patient treatment rooms and equipment, accelerator beamline configuration, and critical facility requirements. The design of the patient treatment rooms must account for diverse criteria to support BNCT clinical processes and potential future expansions, including: possible pretreatment patient CT imaging, surface guided imaging and medical components such as anesthesia equipment. The treatment room sizes were also optimized to consider shielding requirements, primarily based on patient positioning and neutron activation requirements for the ceiling-mounted robotic couch. The Alphabeam beamline was newly configured for CNAO to place each treatment room on either side of the high energy beamline, to minimize the overall facility footprint. While beam optics analysis and Monte Carlo calculations of radiation exposure and component activation for this layout presented some challenges, which have led to architectural and shielding changes, however the ultimate design showed no expected reductions in system performance or compromises on facility safety. The CNAO facility requirements deal with advanced non-linear design of soil-structure interaction and are focused around high performance HVAC, specialized gas venting systems, and the creation of facility-specific walkthrough pathways for personnel safety. Spatial constraints also required creative changes to certain ancillary systems, including electrical cabinets and system control room locations.

The optimization of CNAO's BNCT facility design criteria will facilitate a wide range of future clinical and research applications. Lessons learned and novel ideas from this project have been incorporated into design for future standalone Alphabeam projects.

Keywords:
BNCT, Facility, Design, Architecture, Beamline, Treatment Room

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Confined propagation of slow neutron beams in very thin waveguides with possible application to BNCT

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Guides enabling to focus slow neutrons on spots down to the millimeter (mm) range and their applications to BNCT are discussed in [1]. Here, we shall concentrate on the confined propagation of slow neutron beams along waveguides of smaller transverse dimensions (one micron or somewhat less) [2,3,4].

In [2], discrete guided neutron propagation modes have been experimentally detected in a TiO_2/Ti/Si thin films: the Ti layer (core) had transverse dimension 105 nm and guiding length about 20 mm, while the TiO_2 (15 nm thickness) and Si layers formed the clad with a repulsive potential. This propagation could have applications, among other possibilities, to BNCT of residual very small tumours or cancer cells, after standard BNCT treatments of larger size tumours have been carried out [3, 4]. See Figure 1. Here, we shall report in outline further results on this subject.

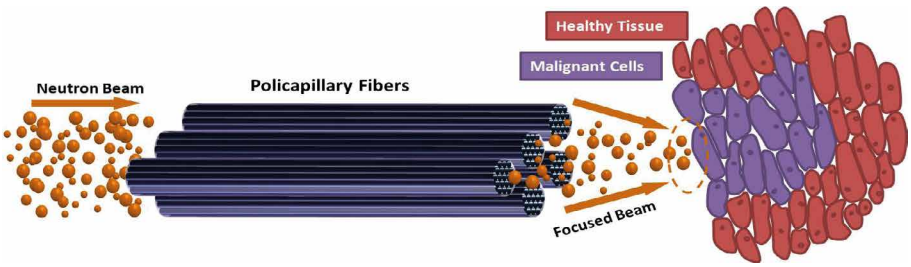

Figure 1. *Schematic representation of neutron transport and focusing on tumors by using waveguides.*

The penetration of a sufficiently massive microscopic particle (a molecule or an atom), into a repulsive material medium (clad) can be regarded as negligible. That yields an approximate vanishing of the particle wave function on the limiting surface (walls) of the clad, thus, described by Dirichlet boundary conditions and has led to reliable quantitative descriptions. For slow neutrons, their confinement into a repulsive clad may be not a large effect, (although the probability of interaction between the neutron and nucleus is not zero, depending on the considered medium). Then, the assumption of a similar Dirichlet boundary condition could be regarded as a zeroth order approximation. The corresponding analysis (by extending nontrivially studies in Electrostatics and Nuclear Physics [5]) has been carried out recently [6] under Dirichlet boundary conditions, based upon Eqs (1) and (2) (containing a Green´s function) below and enabling original algorithms implementations:

$$\varphi(\mathbf{x}) = \varphi_{\mathbf{in}}(\mathbf{x}) + \sum_{\mathbf{i}=\mathbf{1}}^{\mathbf{4}} \int_{\partial\Omega_{\mathbf{i}}} \mathbf{d}\Omega_{\mathbf{i}} \left. \frac{\partial \mathbf{G}(\mathbf{x}-\mathbf{x}'_{\mathbf{i}})}{\partial \mathbf{n}_{\mathbf{i}}} \right|_{\mathbf{x}'_{\mathbf{i}}=\partial\Omega_{\mathbf{i}}} \mu_{\mathbf{i}}(\mathbf{x}'_{\mathbf{i}}) \quad (1)$$

$$G(\mathbf{x}-\mathbf{x}') = -\int\int_{-\infty}^{\infty} \frac{\mathbf{d^2K'}}{\mathbf{(2\pi)^2}} \frac{\mathbf{exp[iK'(x-x')]}}{\mathbf{E}+\mathbf{i}\varepsilon-\frac{\hbar^2}{\mathbf{2m}}\mathbf{K'^2}} \quad (2)$$

The confined propagation of slow neutrons in thin waveguides, by taking into account their penetration into the repulsive clads (accounting for losses) and the formation of propagation modes, is being investigated at present, through new procedures entirely different from those employed when Dirichlet boundary conditions were assumed [6]. In particular, we are applying our techniques, (see Eq. (3), containing also Green´s functions) to the waveguides having Ti cores and their discrete guided propagation modes, considered in [2].

$$\begin{aligned}\psi(\mathbf{x},z) = \psi_{in}(\bar{x}) \quad &+ \int d^2\mathbf{x}_1 \int_0^{+\infty} dz_1 G_1(\mathbf{x}-\mathbf{x}_1, z-z_1) V(\mathbf{x}_1)\phi_{\mathbf{k}}(\mathbf{x}_1)\exp ik_z z_1 + \\ &\int d^2\mathbf{x}_1 \int_0^{+\infty} dz_1 G_1(\mathbf{x}-\mathbf{x}_1, z-z_1) V(\mathbf{x}_1) \times \\ &\int d^2\mathbf{x}_2 \int_{-\infty}^{0} dz_2 G_2(\mathbf{x}_1-\mathbf{x}_2, z_1-z_2)[-V(\mathbf{x}_2)]\psi(\mathbf{x}_2,z_2)\end{aligned} \quad (3)$$

Keywords:
short-scale neutron focusing, possibilities for BNCT of very small tumours

References:

[1] I. Porras in Advances in neutron optics, (M. L. Calvo and R. F. Alvarez-Estrada, editors), CRC Press, Boca Raton, Florida (2020). Chapter 6.
[2] Y. P. Feng et al, Phys. Rev. B49, 10814-10817 (1994).
[3] I. Molina de la Peña et al., 2019, Phosphorus, Sulfur, Silicon Relat. Elem., 194, 956-966 (2019).
[4] I. Molina de la Peña et al in Advances in neutron optics, (M. L. Calvo and R. F. Alvarez-Estrada, editors), CRC Press, Boca Raton, Florida (2020). Chapter 3.
[5] R. Balian and C. Bloch, Ann. Phys., 60, 401-447 (1970).
[6 I. Molina de la Peña et al., J. Mod. Opt., 67, 899-913 (2020).

Neutron sources & facilities

Poster

Modification of the irt-t reactor thermal column for NCT facility development

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Design of facilities for NCT studies based on research nuclear reactors as well as accelerators is quite complicated technical objective. However, these facilities can be used for high-performance treatment of the list difficult-to-treat tumors. In present paper proposed the concept of new NCT facility placed in biological shielding of IRT-T research reactor. The main feature of biological shielding design of IRT-T reactor is the separated shielding concrete blocks which/whose can be removed for further NCT facility development. In order to increase neutron beam intensity thermal neutron-to-fast neutron converter with 4 spent fuel assemblies is used. Safe facility operation is reached by shutter with length of 120 cm made of layers of boron carbide, lead, bismuth and polyethylene with lithium. The BSA design consist of 110 cm air collimator surrounded Pb and MgF_2, Al, AlF_3, Cd filters placed between converter and collimator. Thus, performed calculations shows the possibility of applying present facility for NCT studies with following free beam parameters: $\Phi_{epi} = 0.95 \cdot 10^9$ cm$^{-2} \cdot$s^{-1}, $D_f/\Phi_{epi} = 8.4 \cdot 10^{-13}$, $D_\gamma/\Phi_{epi} = 3.4 \cdot 10^{-13}$.

Measurement of the lithium layer thickness using a proton beam

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In Budker Institute of Nuclear Physics an epithermal neutron source based on a tandem accelerator with vacuum insulation and a solid lithium target for $^{7}Li(p,n)^{7}Be$ reaction was developed. Lithium target is prepared by thermal vacuum evaporation of the thin (typically 60 μm) lithium layer on the water cooled substrate. Average thickness of the layer is calculated knowing the mass of evaporated lithium, but the distribution of the deposited lithium was still unknown. Due to fast oxidation of the lithium in air and its poor mechanical properties direct measurement of the lithium layer thickness is a challenging task. In this work we proposed and realized two different methods for measurement of the lithium distribution over the substrate surface. For this purpose we irradiated different spots of the target by collimated 2 mm proton beam along one axis. Scanning along x-axis is performed using flexible connection between accelerator and lithium target and actuator for target movement. For the first method we used 1.8 MeV protons and measured by a HPGe gamma-spectrometer the intensity of the emitted 478 keV photons in each spot. Lithium thickness distribution is calculated knowing the $^{7}Li(p,p'\gamma)^{7}Li$ reaction cross section and 478 keV photon yield from a thick lithium target that we have measured previously [1]. For the second method we used 2.05 MeV protons scanning over lithium target with average thickness of 7 μm and a neutron dosimeter for neutron yield measurement. In this case neutron yield is directly dependent on lithium thickness. The results of the measurements by two methods are compared and presented in this work. These two measurements are in good agreement with calculations and with each other.

Keywords:
lithium target, proton beam

References:

[1] T. Bykov, D. Kasatov, Ia. Kolesnikov et al. Measurement of the $^{7}Li(p,p'\gamma)^{7}Li$ reaction cross-section and 478 keV photon yield from a thick lithium target at proton energies from 0.7 to 1.85 MeV. These proceedings.

Development of the protective layer for the lithium neutron generating target

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In the Budker Institute of Nuclear Physics an accelerator-based epithermal neutron source is used, among other things, to generate neutrons for BNCT. The neutron beam is generated according to the ^{7}Li(p,n)^{7}Be reaction while the proton beam hits the solid lithium target. The neutron generating target consists of efficiently cooled copper substrate and a thin (typically 60 mcm) lithium layer. In vacuum lithium is thermally evaporated with a controlled thickness on the copper. After a short time being in air the target becomes inapplicable to be used. Several methods were applied to protect lithium layer. The first method was to put the titanium layer over lithium. Titanium was deposited with a controlled thickness using magnetron sputtering. The second method was to deposit highly refined mineral oil over lithium. For this aim, the thermal vacuum deposition was applied. The paper describes the details and comparative characteristics of these technologies.

The study was supported by the Russian Science Foundation (project No. 19-72-30005) and by the Budker Institute of Nuclear Physics.

Keywords:
lithium target, protective layer, accelerating epithermal neutron source

P12

Luminescence of the lithium neutron generating target under proton beam irradiation

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In the Budker Institute of Nuclear Physics an accelerator-based epithermal neutron source is used, among other things, to generate neutrons for BNCT. The neutron beam is generated according to the $^{7}Li(p,n)^{7}Be$ reaction while the proton beam hits the solid lithium target. On the facility the luminescence of the lithium layer under proton beam irradiation was observed using video camera, mounted on a fused quartz glass window. The lithium lines in the luminescence spectrum were determined with a spectrometer. The spectral lines of transitions in lithium correspond to 610,3 nm and 670,7 nm. Hα - hydrogen line with 656,3 nm wavelength was also detected in the luminescence spectrum. As a result of this study the new online diagnostics of a proton beam position on a surface of the solid lithium target was developed and put into operation. The diagnostics is radiation resistant and can be applied in the neutron generation regime.

Keywords:
lithium target, luminescence, accelerating epithermal neutron source

The reported study was funded by RFBR, project number 19-32-90119.

Upgrades of a vacuum insulated tandem accelerator for obtaining requirement voltage without breakdowns

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Epithermal neutron source based on an electrostatic tandem accelerator of a new type - Vacuum Insulation Tandem Accelerator, and lithium neutron target has been proposed and developed at BINP [1] for Boron Neutron Capture Therapy [2] - promising method for treatment of tumors. 2 MeV proton beam was obtained in the accelerator, the neutron generation carried out with bombardment of a lithium target by protons, successful experiments on irradiation of cell cultures incubated in boron medium have been carried out [3], human glioblastoma grafted mice were cured [4]. It is necessary to increase proton energy from 2 to 2.3 MeV [5] to form a neutron beam suitable for the treatment of deep-seated tumors. To do this, it is necessary to provide the high-voltage strength of the accelerator at the potential of 1.2 MV in order to suppress dark currents to an acceptably small value. Two upgrades to obtain the required potential were consistently implemented. At first, the glass rings of the feedthrough insulator were replaced by ceramic ones doubled in height which made it possible to refuse placing the resistive divider inside. Then the smooth ceramic rings were replaced by the new ceramic rings with a ribbed outer surface. Modernization made it possible to obtain the required voltage of 1.15 MV and the proton beam current of 9 mA in the accelerator without breakdowns. The report describes in detail the modernizations carried out, presents the results of the studies, and declares the research plans.

References:

[1] S. Taskaev. Phys. Part. Nucl. 46 (2015) 956-990. doi: 10.1134/S1063779615060064
[2] Neutron Capture Therapy: Principles and Applications. Eds.: W. Sauerwein et al. Springer, 2012.
[3] E. Sato et al. J. Radiol. Res. 59 (2018) 101-107. doi: 10.1093/jrr/rrx071
[4] S. Taskaev. Phys. Part. Nucl. 50 (2019) 569-575. doi: 10.1134/S1063779619050228
[5 L. Zaidi et al. ARI 139 (2018) 316-324. doi: 10.1016/j.apradiso.2018.05.029

The study was supported by the Russian Science Foundation (project No. 19-72-30005) and by the Budker Institute of Nuclear Physics.

P17

Diagnostics of the efficiency of a stripping target of the Vacuum Insulated Tandem Accelerator

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Diagnostics is proposed and developed for measuring the efficiency of stripping a beam of negative ions in a gas stripper of tandem type charged particle accelerator. The coefficient of ion-electron emission during the bombardment of copper by 1 MeV protons was measured. A bending magnet with a horizontal channel was installed which made it possible to place the Faraday cup and absorb a flux of neutrals formed in a stripper as a result of incomplete stripping of negative ions. Diagnostics of the efficiency of a gas stripper was implemented, using the measurement of the electron current emitted from the surface of the Faraday cup when it is bombarded with a directed flux of neutrals and the measurement of the proton beam current with a DC non-destructive current transformer.

Keywords:
vacuum insulated tandem accelerator, epithermal neutron source, gas stripper.

The reported study was funded by RFBR, project number 19-32-90118.

Various diagnostics of the proton beam size on the Vacuum Insulated Tandem Accelerator

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Neutron source consisting of a vacuum insulated tandem accelerator, a thin solid lithium target and a beam shaping assembly is in operation at Budker Institute of Nuclear Physics. Successful biological studies were carried out at the source [1, 2], the content of hazardous impurities in boron carbide ceramic samples developed for ITER was measured [3], radiation testing of optical fibers of the CMS calorimeter laser calibration system for the Large Hadron Collider in high luminosity mode (CERN) is being prepared. The need to ensure long-term stable neutron generation requires the development of diagnostic methods that display real-time state of various subsystems of the neutron source. In this work diagnostics of the proton beam size are described, such as: i) using a blistering effect at proton implantation in metal, ii) using thermocouples, inserted in the lithium target, iii) using a melting of the lithium layer of the target under powerful proton beam, iv) using an activation of the lithium target by berilium-7, v) using video cameras, vi) using an infrared camera, vii) using an effect of the luminescence of the lithium under proton bombardment and viii) using collimator with 2 mm aperture.

Keywords:
vacuum insulated tandem accelerator, epithermal neutron source, beam diagnostics

References:

[1] E. Sato et al., Radiobiological response of U251MG, CHO-K1 and V79 cell lines to accelerator-based boron neutron capture therapy, J. Radiat. Res. 59 (2017) 101.
[2] S. Taskaev, Development of an accelerator-based epithermal neutron source for boron neutron capture therapy, Phys. Part. Nuclei 50 (2019) 569.
[3] A. Shoshin et al., Qualification of Boron Carbide Ceramics for Use in ITER Ports, IEEE Transactions on Plasma Science (2019) doi: 10.1109/TPS.2019.2937605

The study was supported by the Russian Science Foundation (project No. 19-72-30005) and by the Budker Institute of Nuclear Physics.

P21

A feasibility design study for Boron neutron Capture therapy of cancer based on a new deuterium-deuterium (D-D) neutron generator using MCNP code

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The Boron Neutron Capture Therapy (BNCT) is a promising method to treat malignant brain tumors. The basic principle of this technique is to irradiate the boron-containing tumor with epithermal neutrons. Optimization of the Beam Shaping Assembly (BSA) assembly for BNCT has been performed using the Monte Carlo N Particle Transport Code (MCNP6) to shape the 2.45 MeV neutrons that are produced in the axial Deuterium Deuterium (D-D) neutron generator developed at Adelphi Technology, Inc with a radio frequency (RF) driven ion source and nominal yield of about 10^{10} fast neutrons per second. Different materials and Beam Shaping Assemblies (BSA) are investigated and an optimized configuration is proposed. The feasibility of using low enrichment uranium as a neutron multiplier is investigated to increase the number of neutrons emitted from D-D neutron generators, TiF_3 and Al_2O_3 as moderators, Pb as reflector, Ni as shield and Li-Poly as collimator to guide neutrons toward the patient position. Also a simulated Snyder head phantom was used to evaluate dose profiles due to the irradiation of designed beam. As results, characteristic of the neutron beam from the optimized TMC was compared to the recommendation by the International Atomic Energy Agent (IAEA).

Investigation for thickness and material of bolus applicable to boron neutron capture therapy for superficial tumor

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Introduction: University of Tsukuba has developed an accelerator-based BNCT device that produces epithermal neutron beam. We plan to conduct clinical study for head-and-neck cancer and malignant melanoma by using this device in the near future. In Japan, the BNCT for the superficial tumors has been currently conducted in some hospitals where have been installed an accelerator-based BNCT device. During the treatment, to shift the peak dose to skin surface, a 2~3 cm thickness bolus applied in X-ray therapy is usually placed between the beam outlet and the patient. However, the application of the thin bolus in irradiation may give high doses to normal tissue in the deep region. The aim of this study is to investigate the optimal thickness and material of the bolus.

Methods: We performed Monte Carlo analysis. The distribution of normal tissue dose, tumor dose within the water phantom and the irradiation time for each condition were evaluated by changing the thickness of the bolus from 0-10cm, every 1cm. And the material of bolus was also changed to polyethylene and then each dose distribution and irradiation time were calculated. The obtained results were compared.

Results and discussions: According to the BNCT protocols in Japan, we set the maximum normal tissue dose at 10 GyE. When we used the standard method with a bolus of 2 cm thickness of the X-ray bolus, the tumor dose at surface and normal tissue dose at a depth of 2 cm were 62.6 GyE and 8.3 GyE, respectively. And the irradiation time was approximately 29 min. However, when the bolus thickness was increased to 3 cm, the normal tissue dose at the same location was reduced to 7.2 GyE (17% reduction), the tumor dose was slightly reduced to 61.3 GyE while the required irradiation time was extended to 37 min. When the bolus thickness was further increased to 5 cm, the normal tissue dose was further decreased to 6.1 GyE (36% reduction), while the tumor dose remained at a sufficient prescription dose with 57.0 GyE, although the irradiation time was extended to 63 min. In addition, the increase in bolus thickness contributed to the lower contamination ratio of the dose caused by fast neutrons. Fig.1 shows the dose distributions for normal tissue for each thickness of bolus.

Regarding the material of the bolus, applying materials with higher hydrogen content like polyethylene (PE) has the potential to increase the neutron intensity and thus shorten the irradiation time compared to the standard X-ray bolus. For example, using a 3 cm thickness bolus made of PE, the dose distribution of normal tissue was similar to the distribution of 5 cm bolus of X-ray. The irradiation time is able to be shortened to 31 min. When the thickness of PE bolus increases to 4 cm, the dose can be further reduced while keeping the reasonable irradiation time. However, when PE is applied to a bolus in BNCT, we have to work out how to shape it to fit the patient's surface due to the hardness of its material.

Conclusion: In BNCT for superficial tumors, increasing the thickness of the bolus can reduce the dose of normal tissue in the deep region, while reducing the contamination ratio of the fast neutron. Compared to using the same thickness of bolus applied in x-ray irradiation, when irradiating with polyethylene as the material for bolus, the dose to normal tissues can be significantly reduced and the irradiation time can be shortened.

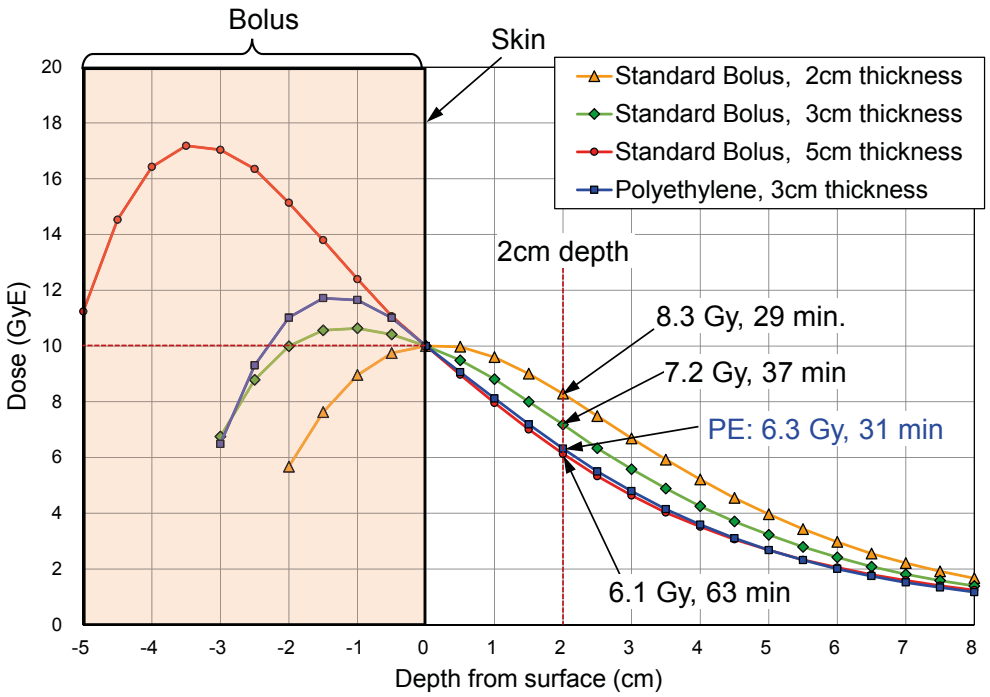

Fig.1 Dose distributions for normal tissue on beam axis for each bolus condition.

Keywords:
Boron Neutron capture therapy, bolus

The new neutron user facility at the University of Birmingham

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The current construction status and future capabilities of the University of Birmingham's new Accelerator Driven Neutron Irradiation Facility (ADNIF) will be presented. The bunker is currently being constructed, with machine delivery at the end of 2021 and commissioning projected to be in early 2022. The bunker will house a 2.6 MeV electrostatic proton accelerator provided by Neutron Therapeutics. Neutron production is based on a solid, rotating lithium target capable of operating for extended periods with beam energies of 2.6 MeV and currents of >30 mA. Total neutron yields from the 7Li(p,n)7Be reaction will exceed 10^{13} neutrons/second.

Initial research will focus on materials damage and both fission and fusion data for the nuclear power industry. However, there are also opportunities for fundamental BNCT research. In addition to the bare target fast neutron beam, a variety of other beam spectra, produced by configurable moderators, will be available. These will include both an epithermal beam, designed to mimic a clinical facility, and a fully thermalised beam.

Detailed beam shaping assembly design is still underway but it is possible to estimate the likely neutron fluences from previous experience with the Dynamitron accelerator facility in Birmingham. It is anticipated that the new facility will produce beam intensities as follows;

a) Dedicated thermal neutron irradiations at >6 x 10^9 n/cm^2/sec

b) Epithermal neutron irradiations producing a peak thermal fluence in a water phantom of approximately 5 x 10^9 n/cm^2/s

A number of proposals to use ADNIF to test new boron compounds, explore fundamentals of BNCT radiobiology and work on new boron imaging techniques are in progress or submitted. These leverage the existing radiobiology and experimental physics resources available at the University of Birmingham, combined with a next-generation accelerator driven source.

In addition to the new facility Birmingham already has a well-established irradiation capability based around it's existing MC40 cyclotron. This machine can provide 10's of uA of protons, deuterons and helium ions at beam energies from a few MeV up to 40 MeV. This allows for a wide range of fundamental radiobiology experiments as well as detector and material characterization. Developments are currently underway to provide very high dose rate control for FLASH radiotherapy work, a new microbeam collimator and in-situ cell cultivation/hypoxia facilities.

Keywords:
user facility, epithermal, thermal, lithium, neutron source

P90

Development of a Sealed Lithium Target for BNCT in Nagoya University

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Nagoya University

Introduction

An accelerator-driven neutron source with a Li target for neutron generation has been developing in Nagoya University. Li is a suitable material to generate low energy neutrons, but Li is difficult to handle as a target due to the following characteristics; low melting point (180 degrees), high chemical activity, and production of the radioisotope Be-7. To resolve these problems, we are developing a sealed Li target with a structure in which Li is covered with a thin Ti foil on a cooling base plate. To ensure the soundness of the sealed Li target, the heat load from the proton beam must be efficiently reduced. In previous studies, high heat removal efficiency could be achieved by inducing turbulent flow by developing a ribbed cooling water channel[1]. We further improved the heat removal performance by investigating the heat transfer coefficient between Li and the target structural materials. In this presentation, in order to evaluate the durability under beam irradiation conditions (~ 7 MW / m^2), we will report the experimental results of long-term proton beam irradiation to a sealed Li target and the generated thermal neutron flux.

Materials and Methods

The Li target was irradiated with proton beam of 1.8 MeV which dose not activate the Li for 46 hours in a week (5.6 MW / m^2). The temperature inside the target was measured by multiple thermocouple sensors inserted from the back of the Li target. The target surface temperature was measured using images from an infrared camera. The damage to the Ti foil and melting of the Li during beam irradiation was monitored by a quadrupole mass spectrometer for Ti and Li vapor in the beam line, and the surface condition of the Ti foil was evaluated with a IRcamera after the beam irradiation test. In addition, the thermal neutron flux was measured to verify that there was no change in the amount of neutrons generated during proton beam irradiation. In the measurement of the thermal neutron flux, Au foils were placed in the water tank and irradiated at 2.8 MeV and 4 mA. The Au foil after irradiation was measured with a germanium detector, and thermal neutron flux evaluation was performed using the Au foil activation method.

Results

In the durability evaluation experiment of the target, the surface temperature during proton irradiation was measured to be about 60 degrees, which was kept below the melting point of Li (180 degrees). In addition, Ti and Li vapors does not detected by the quadrupole mass spectrometer. And no damage was observed on the surface of the titanium foil after irradiation, and no leakage of Li was observed. From these results, it was verified by experiments that the protons could be irradiated with beam power (5.7 MW / m^2) for about 50 hours to maintain the seal with Ti foil. In an experiment in which the Li target was irradiated at 2.8 MeV and 4 mA, the maximum thermal neutron flux was 2.5×10^8 n / cm^2 / s. In addition, no damage to the surface of the titanium foil, leakage of Li, or change in the amount of neutrons generated after irradiation was observed.

Keywords:
neutron source, lithium target

References:

[1] Sachiko Yoshihashi, et al., High Heat Removal Technique for a Lithium Neutron Generation Target used for an Accelerator-driven BNCT System, Journal of Instrumentation,

A Theoretical and Experimental Test On the Performance of an Integrated Activation Device for Neutron Spectrum Confirmation at THOR-BNCT

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BNCT is provided to emergency treatment at THOR-BNCT in almost weeks nowadays. However, the neutron spectrum cannot be examined by the current QA/QC measures and the conventional foil activation takes 5 days (1188 min in irradiation) to re- measure it. Considering the tight schedule of THOR-BNCT to provide neutron beam, another solution is urgently needed.

To check rapidly whether the neutron spectrum remains eligible to BNCT standard, an integrated activation device, composed of PMMA phantom and eight foils (Sc, La, Cu, InAl, Au, Co, Ni, In) is developed and by which the following can be achieved: beam time required is reduced to 30 minutes; all the subsequent measurements can be finished within a day using single HPGe detector.

7 experimental tests have been conducted since June, 2020. All the experiment results show that this Device has a stable and consistent performance compared with corresponding MCNP simulation based on previously established beam characterization work.

Following sensitivity test on spectrum, which alters the portion of spectrum or tilts the spectrum, proves that the Devise does react and signal an indication following the spectrum variation. If the ratio of epithermal group to total spectra varies beyond +3% or -6%, or if the spectrum is slightly softened or hardened, this device can signal a warning about it.

Overall, this device yields spectrum information accurate enough while reducing the time cost to a single day. It is very suitable for solving the issue mentioned above.

Thus, the incorporation of this detector into QA/QC measures for BNCT is recommended.

Keywords:

Foil Activation, Beam Characterization, Quality Assurance, Quality Control

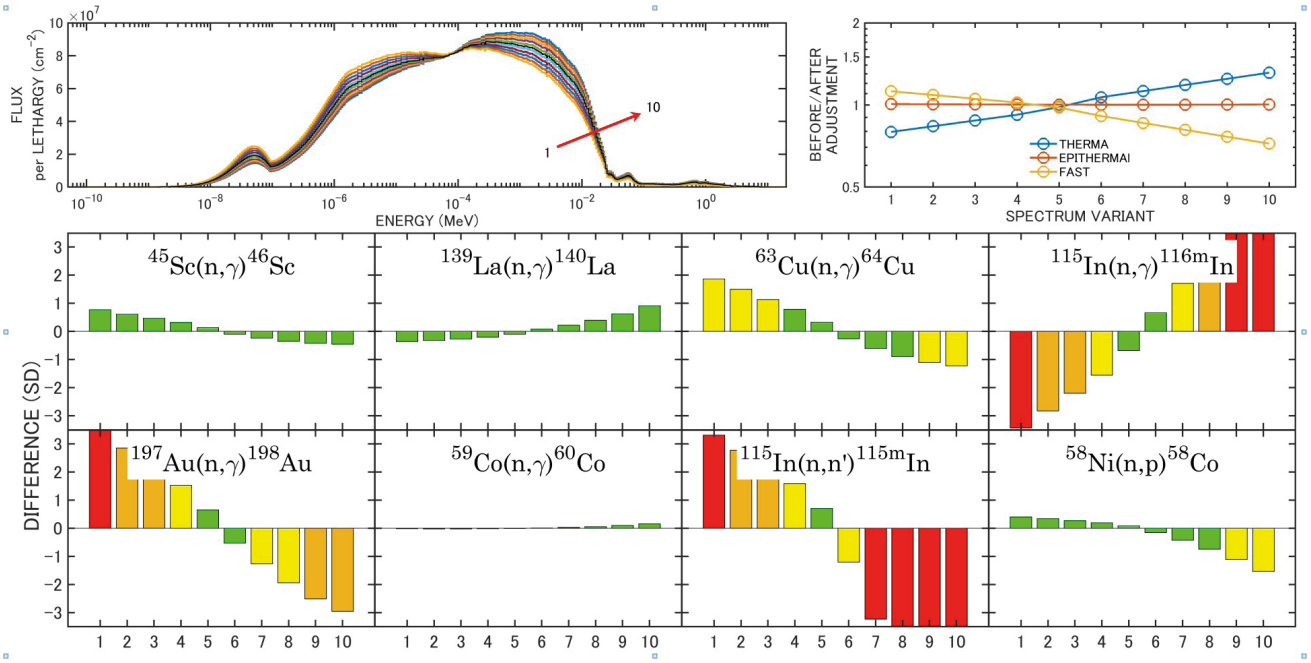

Figure 1: Sensitivity Test on Spectrum. On the top left are 10 spectrum variants; 1 means most-softened and 10 means most-hardened. On the top right are group flux change. The bar chart shown below is the corresponding foil reaction rate change in the unit of standard deviation.

Measurement of neutron and gamma dose rates from a lithium target at proton energies up to 2.3 MeV and lithium thicknesses from 1 to 208 µm

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Boron neutron capture therapy, which requires an intensive beam of neutrons of the epithermal energy range, is considered to be a promising treatment method for malignant tumors. It is generally accepted that neutron generation as a result of $^{7}Li(p,n)^{7}Be$ and $^{9}Be(p,n)^{10}B$ threshold reactions at proton energies in the region of 2-3 MeV allows to form a neutron beam, which meets the requirements of BNCT to the greatest extent. At the Budker Institute of Nuclear Physics, an epithermal neutron source consisting of a vacuum insulated tandem accelerator to produce a proton beam and a lithium target for neutron generation has been proposed and created. It is known that the interaction of protons with lithium produces 478 keV gamma-ray flux comparable to that of neutrons. To reduce this undesirable gamma-ray flux, the thickness of the lithium layer is chosen so that the proton energy at the layer outlet is slightly lower than 1,882 MeV, the $^{7}Li(p,n)^{7}Be$ reaction threshold. The report presents and discusses the results of measuring of neutron and gamma dose rates from the lithium target at proton energies up to 2.3 MeV and lithium thicknesses from 1 to 208 µm. It was found that using a thin lithium layer reduces the undesirable dose of gamma radiation by 2 times without reducing neutron yield.

The study was supported by the Russian Science Foundation (project No. 19-72-30005) and by the Budker Institute of Nuclear Physics.

P20

Measurement of the 7Li(p,p'γ)7Li reaction cross-section and 478 keV photon yield from a thick lithium target at proton energies from 0.7 to 1.85 MeV

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A cross section of inelastic scattering of protons on atomic nuclei of lithium and an yield of 478 keV photons from a thick lithium target has been measured at proton energies from 0.7 to 1.85 MeV. The study was conducted on a vacuum insulated tandem accelerator using targets with various thicknesses of lithium layer. The intensity of the emitted photons was measured by a gamma-spectrometer with high purity germanium detector. The spectrometer was calibrated on full and relative sensitivity by reference radionuclide sources of photon radiation. The measurement results were compared with those presented in the EXFOR nuclear reaction database and published in open sources. The reliability of the results of previous studies was assessed. The obtained data on the $^{7}Li(p,p'\gamma)^{7}Li$ reaction cross section and 478 keV photon yield from a thick lithium target are most accurate. The report presents the results of the study and notes the importance of the results for treatment planning.

The study was supported by the Russian Science Foundation (project No. 19-72-30005) and by the Budker Institute of Nuclear Physics.

Chemistry and pharmacology

Chemistry and pharmacology

Synthesis of functional polymers boosting therapeutic potential of *p*-boronophenylalanine and analysis of the effect of their physicochemical properties on pharmacokinetics

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p-Boronophenylalanine (BPA) has been the most powerful boron drug in clinical boron neutron capture therapy (BNCT), because it can accumulate selectively within tumors by being recognized by LAT1 amino acid transporters overexpressed on many tumor cells. However, antiport mechanism of LAT1 causes unfavorable efflux of intracellular BPA due to exchange with extracellular amino acid including tyrosine [1], resulting in decrease of intratumoral boron concentration during thermal neutron irradiation and compromising therapeutic efficiency.

In this regard, we recently found that poly(vinyl alcohol) (PVA) can form a complex with multiple BPA molecules through boronate esters in water and that the PVA-BPA complex could be internalized into the LAT1-positive cancer cells through LAT-mediated endocytosis, which led to enhanced cellular uptake and prolonged retention in the tumor cells by avoiding the aforementioned efflux [2]. In murine subcutaneous tumor models, PVA-BPA exhibited the efficient accumulation selectively within tumors and prolonged intratumoral retention upon intravenous injection, thereby accomplishing the significantly enhanced BNCT effect. To further investigate the validity of the aforementioned concept and the effect of physicochemical properties of polymers on pharmacokinetics, we synthesized a poly(ethylene glycol)-poly(L-lysine) (PEG-PLys) derivative having fructose moieties that can form boronate esters with BPA in the side chain [3]. The fructose-functionalized polymer, termed PEG-P[Lys/Lys(fructose)], could form the complex with BPA like PVA-BPA and exhibited the prolonged intratumoral retention. Importantly, PEG-P[Lys/Lys(fructose)]-BPA showed quicker clearance from the bloodstream than PVA-BPA due to the slightly cationic property, which may reduce the possible unfavorable radiation damage to the normal tissue. It should be noted that another PEG-PLys derivative functionalized with gluconate moieties was also synthesized; however, the gluconate-functionalized polymer exhibited the different pharmacokinetic behavior from that of PEG-P[Lys/Lys(fructose)].

This presentation reports and summarizes these polymer-BPA systems for tumor-targeted drug delivery, thereby indicating the future prospects of designing boron drugs.

Keywords:
p-boronophenylalanine (BPA), LAT1, drug delivery system, polymer

References:

[1] A. Wittig, et al., Mechanisms of transport of *p*-borono-phenylalanine through the cell membrane in vitro, ***Radiat. Res.*** 153 (2) (2000) 173-180.
[2] T. Nomoto, et al., Poly(vinyl alcohol) boosting therapeutic potential of *p*-boronophenylalanine in neutron capture therapy by modulating metabolism, ***Sci. Adv.*** 6 (4) (2020) eaaz1722.
[3] T. Nomoto, et al., Fructose-functionalized polymers to enhance therapeutic potential of *p*-boronophenylalanine for neutron capture therapy, ***J. Control. Release*** 332 (2021) 184-193.

Synthesis of 10B-containing compounds binding to amyloid β aggregates for Alzheimer's disease-BNCT

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The therapeutic agents for Alzheimer's disease that have been used clinically so far are mainly cholinergic enzyme inhibitors. They have the effect of improving symptoms temporarily. In recent years, the development of molecular-targeting drugs which prevent the deposition of the produced amyloid β monomer has been promoted. However, it can be easily inferred that it is extremely difficult to remove the amyloid β aggregates once deposited. In this study, we synthesized several ^{10}B-containing compounds with specific binding properties to amyloid β protein and the blood-brain barrier permeability and we observed fragmentation of amyloid β aggregates by BNCT in in vitro studies. These results suggest the effect of BNCT on the treatment of Alzheimer's disease. Clinically cognitive functions may be restored by removal of amyloid plaques and subsequent clinical rehabilitation. BNCT is expected to expand into the new fields.

An attempt was made to synthesize some boron carrier compounds used in BNCT. As a boron ligand compound that specifically binds to amyloid β protein, we searched for synthetic pathways in flavone derivatives, styrylchromone derivatives, aurone derivatives, chalcone derivatives, benzothiazole derivatives, and stilbene derivatives. We have developed a synthetic route that can efficiently introduce ^{10}B-atoms into these compounds. Several ^{10}B-introduction methods have been attempted to (i) Grignard reaction or lithiation for borylation in the first process of a series of reactions, (ii) borylation by pinacolborane or bis(pinacolato)diboron using palladium catalyst in the final reaction process, and (iii) use other borylation reagents. For example, in the case of the synthesis of 4'-dimethylamino-6-^{10}B-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) flavone (^{10}B, 99%), there are several synthetic procedures, and it was found that the method using palladium catalyst with some ligands is better. This method allowed borylation in the yield of 32% (mol%) in the reaction for 160 min when ^{10}B-pinacolborane (^{10}B, 99%) was used as the starting material.

The effect of fragmentation of each boron ligand was evaluated using 180 - 245 kDa or more agglutinating protein which amyloid β monomer (1-42) was artificially aggregated. As a method, the accelerator-based neutron source, CICS-1 (manufactured by CICS, Inc.) for neutron capture therapy, was used to irradiate amyloid β aggregates previously incubated with a boron ligand compound. After that, we examined the fragmentation of amyloid β aggregates by SDS-PAGE method. As a result, a reduction in agglutinating protein of 180 - 245 kDa or more could be observed at irradiation dose of 3Gy (physical dose) in each boron containing compounds. On the other hand, no reduction occurred in the vehicle-only nor the lane in which boric acid was adjusted to the same ^{10}B concentration.

We focused on boron-containing organic compounds that can selectively fragment amyloid β plaques at the micron level. These results indicate that BNCT can be used for the non-DNA dependent elements other than cellular target. The compounds selectively bind to amyloid β plaques and they do not damage non-affinitive neurons. It provides an opportunity to promote the reconstruction of neural circuits [1] and the remodeling neural networks [2]. Based on the concept of PET-BNCT [3], the combination of relevant tracers used for PET analysis may efficiently contribute to development of Alzheimer's disease-BNCT method with the presented ^{10}B-boron ligands.

Keywords:
Alzheimer's disease-BNCT, ^{10}B-boron ligands, amyloid β aggregates.

References:

[1] Y. Imahori, et al., Neural features of recovery from CNS injury revealed by PET in human brain, Neuroreport 10(1):117-121(1999).
[2] M. Kondo, et al., Aberrant plasticity in Alzheimer's disease, Neuroreport 10(7):1481-1484(1999).
[3] Y. Imahori, et al., A basic concept for PET-BNCT system. In: Y. Mishima (ed), Cancer Neutron Capture Therapy, pp.691-696. New York: PlenumPress,1996.

Sugar derivatives as theranostic agents for BNCT

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Recent advances in the development of accelerator-based in-hospital neutron source to replace the previously required nuclear reactor, urge the advancement of the research towards the identification of new agents able to selectively accumulate enough boron in tumor tissues for clinical use. Currently, two low molecular weight boron-containing compounds, sodium mercaptoundecahydro-closo-dodecaborate (BSH) and borylphenylalanine (BPA) are used in BNCT, having some therapeutic effect in patients bearing various kinds of tumors, although with suboptimal tumor selectivity.

Among the different strategies explored for tumor delivery and targeting, we have been mainly involved in the use of boron-containing sugar derivatives. A major issue in the development of treatment protocol is the real-time tracking of the BNCT agent *in vivo* which would allow an image-guided radiation therapy.

We herein present the synthesis of new compounds containing boron moieties linked to saccharidic structures as potential agents for BNCT. We developed new potential theranostic agents containing a trifluoroborate moiety that can furnish at the same time the boron atom required for BNCT and an ^{18}F to for monitoring the compound *in vivo*. The fluorine atoms of the trifluoroborate group can be exchanged by an ^{18}F isotope which can be exploited as a positron emitter, guiding BNCT in an orthogonal modality. ^{18}F is a radiotracer commonly used for Positron Emission Tomography (PET) that permits the tracking of compounds *in vivo*, allowing the visualization of the compound biodistribution in the body and its accumulation in the tumor.

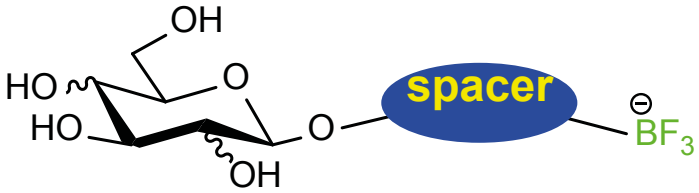

Figure 1. *General structure of the synthesized compounds*

To ensure a higher tumor affinity *vs* normal cells, trifluoroborate will be conjugated to molecules able to selectively target cancer cells. In our compounds, sugars represent the substructures of choice with the hypothesis to exploit their higher consumption by malignant cells and their selective uptake thanks to GLUT transporters.

Keywords:
sugars, trifluoroborate, PET tracer, GLUT

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Radiolabeled Cobaltabis(dicarbollide) Anion-Graphene Oxide Nanomaterials as Potential Theranostic Agents for BNCT and In Vivo Bioimaging

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Metallacarboranes, particularly the cobaltabisdicarbollide (COSAN, $[Co(C2B9H11)2]^-$), are anionic boron clusters with exceptional physicochemical properties and low toxicity in biological systems. The hydrophobic nature of COSAN confers high amphiphilicity, which accounts for its good solubility and its capacity to self-assemble into micelles and monolayer vesicles in aqueous media. We have previously demonstrated that COSAN derivatives are able to cross the lipid bilayer membrane of cells and accumulate in different types of living cells. [1] COSAN derivatives have been covalently linked to dendrimers, gold nanoparticles or SWCNTs, giving rise to materials with enhanced dispersibility, electrochemical features, cellular uptake and intracellular boron release. All these properties, together with the high boron content make this anion and their derivatives ideal candidates for BNCT.[2,3] On the other hand, graphene oxide (GO) has aroused as attractive platforms as they presents high biocompatibility and prolonged blood circulation times. Then, our aim is to combine the advantages of COSAN and GO to develop boron- enriched nanomaterials, which also can be tagged with radioisotopes in order to assess tumor accumulation of the hybrids in both in vitro and in vivo experiments.

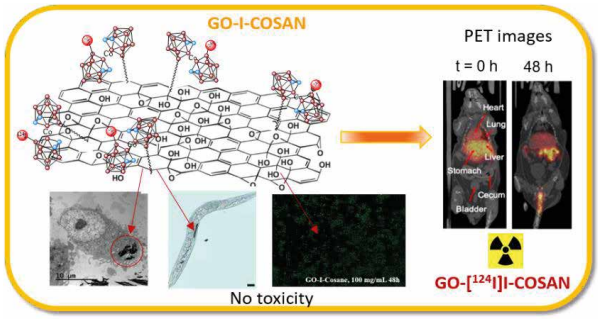

Figure 1. *In vitro and in vivo properties of the boron rich nanomaterial*

We have efficiently developed a new nanomaterial (GO-I-COSAN, Fig. 1) based on graphene oxide (GO) functionalized with radiolabeled COSAN (I-COSAN) and demonstrated that our nanomaterial can potentially act as a theranostic agent for diagnosis (radioimaging) and therapy (anticancer agent for BNCT).[4] TEM analyses confirm the internalization of the nanomaterial by cells and its accumulation in the cytoplasm, without causing changes neither in the size nor in the morphology of cells. The GO-I-COSAN does not show cytotoxicity *in vitro* for HeLa cells, with a cell viability greater than 90 %. Furthermore, GO-I-COSAN is ingested by *C. elegans* resulting in a survival rate of around 100 %, revealing the absence of toxicity *in vivo* for the worms and

supporting the results observed in the in-vitro studies. Radiolabeling of the material with the positron emitter ^{124}I was achieved via isotopic exchange of the I-COSAN to obtain [^{124}I]I-COSAN followed by its grafting onto GO. Biodistribution studies by Positron Emission Tomography (PET) indicate accumulation of the nanomaterial in the liver at early time, as well as accumulations in lungs and kindness. The nanomaterial shows radiochemical stability *in vivo* and relative long circulation time. Taking into account that long-circulating nanomaterials tend to accumulate in tumors to a certain extent due to enhanced permeability and retention (EPR) effect, it is reasonable to assume that our nanomaterial would show important tumor uptake, resulting in a high concentration of boron atoms in the tumor tissue, which is a requirement for BNCT. Notably, a favorable biodistribution profile suggests the potential use of this nanomaterial as a theranostic agent for in vivo bioimaging and boron carriers for BNCT.

Keywords:
metallacarboranes, graphene oxide, boron delivery, BNCT, PET, radiolabeling

References:

[1] a) Chaari, M.; Gaztelumendi, N.; Cabrera-González, J.; Peixoto-Moledo, P.; Viñas, C.; Xochitiotzi-Flores, E.; Farfán, N.; Ben Salah, A.; Nogués, C.; Núñez, R. *Bioconjugate Chem.* **2018**, *29*, 1763. b) Cabrera- González, J.; Muñoz Flores, B. M.; Viñas, C.; Chávez-Reyes, A.; Dias, H. V. R.; Jiménez Pérez, V. M.; Núñez, R. *Chem. Eur. J.* **2018**, 24, 5601.

[2] Couto, M.; Alamón, C.; García, M. F.; Kovacs, M.; Trias, E.; Nievas, S.; Pozzi, E.; Curotto, P.; Thorp, S.; Dagrosa, M.A.; Texidor, F.; Viñas, C. *Cells*, **2020**, *9*, 1408; doi:10.3390/cells9061408.

[3] a) Barth, R. F.; Mi, P.; Yang, W. *Cancer Commun.* **2018**, *38:36;* doi: 10.1186/s40880-018-0280-5. b) Hu, K.; Yang, Z.; Zhang, Xie, L.; Wang, L.; Xu, H.; Josephson, L.; Liang, S. H.; Zhang, M.-R. *Coord. Chem. Rev.* **2020**, *405*, 213139.

[4 Ferrer-Ugalde, A.; Sandoval, S.; Pulagam, K. R.; Muñoz-Juan, A.; Laromaine, A.; Llop, J.; Tobias, G.; Núñez. R. ACS Appl. Nano Mat., **2021**, *4*, 1613-1625.

Development of an albumin-based boron delivery system for neutron capture therapy

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In 2020, accelerator-based BNCT for head and neck cancer using L-BPA was approved by the Pharmaceuticals and Medical Devices Agency in Japan, making BNCT more accessible treatment. L-BPA is known to actively accumulate into tumor cells thorough L-type amino acid transporter 1 (LAT-1). However, there are many cancers with low L-BPA accumulation, therefore there is a need for new boron drugs that exhibit a cancer-selective uptake mechanism different from that of L-BPA. For this requirement, we have been working on the development of drug delivery systems with novel low-toxic boron compounds which enable the necessary accumulation in tumor cells that have shown poor uptake of L-BPA.

Folic acid (FA) is a natural ligand of folic acid receptor (FR) that is known to be overexpressed in several tumor cells, including glioblastoma cells. Previously, we developed pteroyl-*closo*-dodecaborate conjugate (PBC) and evaluated its cytotoxicity and intracellular uptake.[1] In addition, we administrated PBC into F98 glioma-bearing rats directly via convection-enhanced delivery (CED). Inductively coupled plasma atomic emission spectroscopy (ICP-AES) showed higher boron concentrations in tumor than ipsilateral and contralateral brain.[2] Neutron irradiation experiments showed the similar survivals of both L-BPA (i.v.) and PBC (CED) but the extension of median survival of the mice with combination of L-BPA (i.v.) and PBC (CED), suggesting that PBC and L-BPA accumulate into F98 glioma cells through the different uptake mechanisms. On the other hand, when PBC was administered by intravenous injection, the boron concentration in tumor was not sufficient for BNCT, and most of the PBC accumulated into the liver (unpublished results). Base of these observations, we considered that improving the retention of PBS in the blood was essential for increasing the intratumor boron concentration.

To this end, we designed a new delivery system that utilizes albumin as a boron carrier. Albumin is a major component of blood and has been utilized in many drug deliveries because it accumulates into tumors due to enhanced permeability and retention (EPR) effect. We developed pteroyl-*closo*-dodecaborate conjugate-iodophenyl (PBC-IP), which consists of an iodophenyl group as an albumin ligand,[3] a *closo*-dodecaborate as a boron source, and a pteroyl group as the FA skeleton interacting with FRs. We expected that PBC-IP would show more efficient antitumor effect than PBC by following mechanisms: intravenously injected PBC-IP would form a complex with endogenous albumin in the blood, accumulate in tumor tissue due to the EPR effect, and be taken up by cancer cells through the interaction of the pteroyl group and FRs overexpressed on the cell surface.

PBC-IP was synthesized from three components, 4-iodophenyl butyric acid, pteroyl azide, and *closo*-dodecaborate-containing amine,[4] in a total of 12 steps. Cell-based assays using FR-positive U-87MG cells revealed that boron accumulation of PBC-IP was twice higher than that of L-BPA. Furthermore, the significant tumor growth suppression was observed in U-87MG xenograft models at a dose of 10 mg[^{10}B]/kg of PBC-IP after neutron irradiation.

References:

1. Nakagawa F., *et al.*, "Water-soluble *closo*-dococaborate-containing pteroyl derivatives targeting folate receptor-positive tumors for boron neutron capture therapy" *Cells,* **2020,** *9*, 1615.
2. Kanemitsu T., *et al*., "Folate receptor-targeted novel boron compound for boron neutron capture therapy on F98 glioma-bearing rats" *Radiat. Environ. Biophys.* **2019,** *58*, 59-67.
3. Dumelin C. E., *et al.*, "A portable albumin binder from a DNA-encoded chemical library" *Angew. Chem. Int. Ed. Engl.* **2008,** *47*, 3196-3201.
4. Nakamura H., *et al*., "closo-Dodecaborate-conjugated human serum albumins: preparation and in vivo selective boron delivery to tumor" *Pure Appl. Chem.*, **2018**, *90*, 745-753.

Investigation of cellular response to TMA (trimethylammonium 1-mercapto-1-carbadodecaborate) - a new, pharmaceutical precursor for the Boron Neutron Capture Therapy

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In the Boron Neutron Capture Therapy (BNCT) searching for new carriers of boron-10 is both necessary and important [1, 2]. This study aimed to compare TMA (trimethylammonium 1-mercapto-1-carbadodecaborate) chemical with a clinically used compound - BSH (di-sodium undecahydro-mercapto-closo-dodecacarborate) in BNCT (Boron Neutron Capture Therapy) through investigation of their influence on cell viability, cytotoxicity and apoptotic effects in a panel of the selected human cancer cell line. MTS assay was used to evaluate cytotoxic effects. Triplex assay was used to assess viability, cytotoxicity and apoptotic progression. TMA compound showed a significant cytotoxic effect in cancer cells with the concentration in 2 μg/ml compared to BSH. At the same time, cancer cells activated self-protective mechanisms by increasing the activity of live-cell proteases. Viability of the cells correlated with the cytotoxicity of the compounds tested. The apoptotic pathway was initiated at a nanomolar concentration. The apoptosis pathway depended on the concentration of the compound tested, not on the incubation time. TMA caused an increase in the percentage of late apoptotic cells in all tested cancer cells, similarly to BSH. These results suggest that the compound TMA might be a promising agent for cancer-targeted radiotherapy, as is BNCT. The chemical properties of the TMA compound were also tested in this project. Further structural modifications with i.e. neuroproteins derivatives may create a targeted promising anticancer agent.

We are planning to continue our research and make attempts to bind selected boron compounds with selective carriers.

Keywords:
BNCT, coupling reaction, boron clusters, biological response

References:

[1] W.A.G. Sauerwein, A. et al. *Neutron Capture Therapy: Principles and Applications*, 2012, Springer-Verlag, Heidelberg
[2] R.L. Moss, *Appl Radiat Isot.* vol. 88:2-11, 2014.

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O65

Synthesis and Preliminary *In-Vitro* Studies of Novel Boronated Monocarbonyl Analogues of Curcumin (BMAC) for Antitumor and β-Amiloyd Disaggregation Activity

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Curcumin is currently being investigated for its capability of treating many types of cancer and to prevent the neuron damage observed in Alzheimer's disease (AD).[1] However, its clinical use is limited by its low stability and solubility in aqueous solutions. A great deal of effort has therefore been devoted to the synthesis of Curcumin analogues, among them mono carboranyl analogues of Curcumin (MAC), in which a carbonyl group replaces the β-diketone functionality.[2] MAC have attracted considerable attention because they feature greater stability than Curcumin, thus retaining or even increasing biological activity, while improving pharmacokinetics too.

In order to combine the natural efficacy of Curcumin against β-amyloid aggregation or cancer cells with the selective destructive effects provided by BNCT (Boron Neutron Capture Therapy), we recently synthetized hybrid compounds which contain both a Curcumin-related moiety and a boronated portion which can be exploited to destroy brain plaques of AD and/or tumor cells by neutron irradiation, see Figure 1.[3]

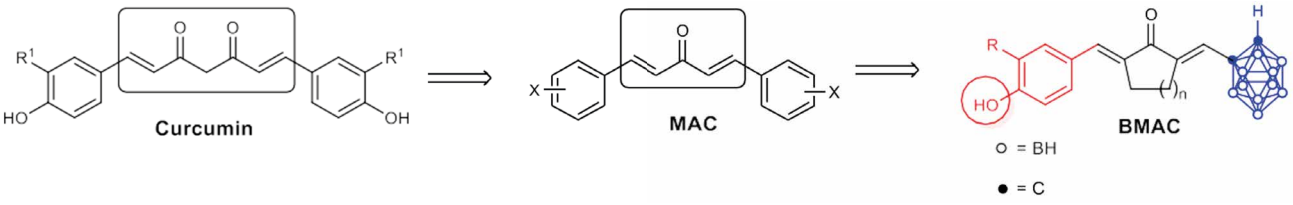

Figure 1

In Figure 1, the general structure of Boronated Monocarbonyl Analogues of Curcumin (BMACs) is reported. These compounds feature a carbonyl group replacing the Curcumin β-diketone functionality, and an *ortho*-carborane, an icosahedral boron cluster, substituting one of the two phenolic rings. We synthesized and assessed *in vitro* BMAC antitumor activity against MCF7 and OVCAR-3 and mesothelioma cell lines (ZL34, AB22) and we compared to that of Curcumin and the corresponding MAC derivative. In all cell lines, BMACs showed similar efficiencies to that of MAC and superior to that of Curcumin. Notably, BMAC containing two -OH moieties was more efficient than Curcumin. The β-amiloyd disaggregation activity of BMACs was also tested exploiting Thioflavin T fluorescent assay to evaluate the inhibition of the formation of fibril aggregates. Also in this case, the presence of a second –OH enhanced the binding efficacy with β-amyloid aggregates. The preparation of other BMACs where a rigid cycle is introduced is under study. Moreover, thanks to the presence of the carborane cage, irradiation experiments will be carried out, thus coupling the BMAC antitumor and β-amiloyd disaggregation effect with BNCT.

Keywords:
Curcumin, monocarbonyl analogues of Curcumin, carboranes, BNCT, Alzheimer's disease, cancer

References:

[1] S. Vahid, S. Amirhossein, H. Hossein, Phytother. Res. 32(6) (2018) 985-995; I.W. Hamley, Angew. Chem., Int. Ed. Engl. 46(43) (2007) 8128-8147. [2] F.C. Rodrigues, N.V. Anilkumar, G. Thakur, Eur. J. Med. Chem. 177 (2019) 76-104. [3] E. Azzi, D. Alberti, S. Parisotto, A. Oppedisano, N. Protti, S. Altieri, S. Geninatti-Crich, A. Deagostino, Bioorg. Chem. 93 (2019) 103324.

O78

The improvement of tumor accumulation by polymeric nanocarriers on gadolinium neutron capture therapy

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Introduction

Neutron capture therapy (NCT) utilizes secondary radiation particles produced after neutron capture reaction in killing tumor cells. Compared with boron, gadolinium (Gd) is not only easier to capture neutron (66 times higher than boron), but gadolinium compounds can be used as contrast agents for magnetic resonance imaging (MRI), therefore, diagnostic treatment can be expected.

Nanoscale drug carriers are a promising way to promote the accumulation of Gd agents in tumors through the enhanced permeability and retention (EPR) effect. While diverse nanocarriers for Gd delivery have been reported [1], a suitable system has yet to be established. In order to design a system with high Gd loading capacity that avoid Gd leakage, long tumor retention time, we developed a series of polymers.

Method

A series of polymers based on poly (aspartic acid) (P(Asp)) and PEG were developed. Homo-P(Asp), PEG_{272}-P(Asp) and PEG_{454}-P(Asp) were synthesized by ring opening polymerization (ROP) of β-Benzyl-L-aspartate N-carboxy-anhydride (BLA-NCA) to homo-poly(β-benzyl-L-aspartate), PEG_{272}-poly(β-benzyl-L-aspartate) and PEG_{454}-b-poly(β-benzyl-L-aspartate) and subsequent deprotection with NaOH. These polymers were used to conjugate DOTA chelating moieties for introducing Gd, resulting in homo-P(As-DOTA), PEG_{272}-P(Asp-DOTA) and PEG_{454}-P(Asp-DOTA) (Figure 1a). After that, Gd release and cytotoxicity were evaluated.

Besides, the cellular uptake was evaluated against Murine colon adenocarcinoma 26 (C-26 cells) and the Gd concentration in plasma and tumors was measured by ICP-MS.

To evaluate the efficacy for GdNCT, we injected the polymers in mice bearing C-26 tumors. After 24h, the tumors were irradiated with a thermal neutron beam ($2x10^{12}$ n/cm^2) for 1h. The tumor size was measured every 3 or 4 days after irradiation.

Result

The Gd-DOTA conjugated polymers were stable sufficiently for restricting Gd leakage in bloodstream, since 1.88%, 1.42% of free Gd were released from PEG_{272}(PEG_{272}-P(Asp-Gd-DOTA)) and PEG_{454}(PEG_{454}-P(Asp-Gd-DOTA)) after 72h. Besides, the viabilities of the C-26 cells were all more than 80% after exposure for concentrations up to 100μM, which supported the safety of polymers.

For cellular uptake, the results indicated the gradual uptake of both polymers. After 24h incubation, the cellular uptake of PEG_{272} was 2-fold higher than that of PEG_{454}.

Both PEG_{272} and PEG_{454} showed prolonged availability, with over 50% and 70% of Gd were remaining in circulation 1h after administration, respectively. These values are much higher than that reported for free Gd-DTPA (only 10% after 5min) [2]. The tumor accumulation of PEG_{454} after injection gradually increased from 2.4% to 3.8% and remained constant until 24h. Meanwhile, the tumor levels of PEG_{272} gradually increased to 2.2% and remained constant until 24h.

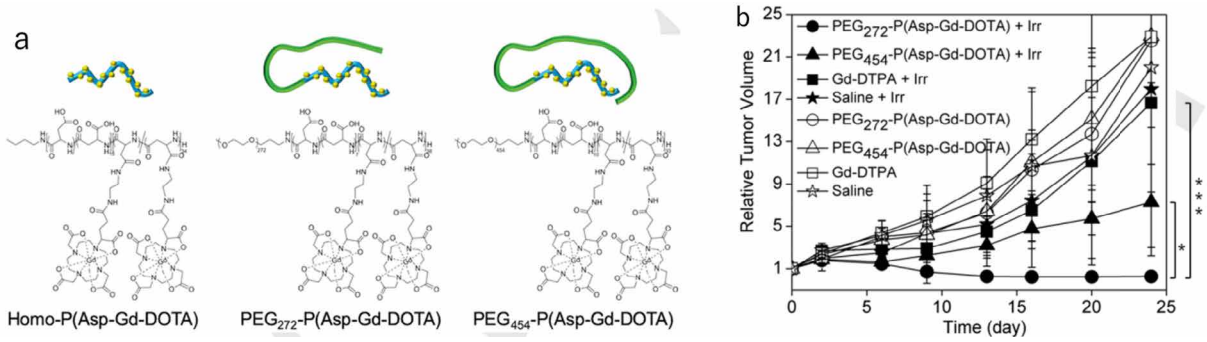

Figure 1. *a. Series of polymers b. Anti-tumor effect*

From the results of antitumor effect after GdNCT (Figure 1b), the growth rate was significantly inhibited compared with non-irradiation group. Compared with $PEG_{454,}$ PEG_{272} showed more potent antitumor ability. From day 9, the relative tumor volume became smaller than before irradiation, and until day 24, the relative tumor volume was 0.27 of the initial size. The enhancement of the antitumor activity of PEG_{272} could be attributed to the higher cellular uptake, as intracellular delivery of Gd has been indicated to be critical for effective cell killing.[3]

Conclusion

Gd-DOTA-conjugated PEG-P(Asp) block copolymers were successfully developed. Neutron irradiation promoted effective suppression of the tumor growth rate by these polymers. PEG_{272} had higher cellular uptake and PEG_{454} remained more in tumor. Between them, PEG_{272} had better anti-tumor effect. Our results support the potential of PEG-P(Asp-Gd-DOTA) systems as promising agents for GdNCT.

Keywords:
Drug Delivery System, Block Copolymers, MRI, Gadolinium Neutron Capture Therapy

References:

[1] Y. Xiao. *Magn. Reson. Imaging*. **2015**, 33, 822–828
[2] H. J. Weinmann. *Am. Roentgen Ray Soc*. **1983**, 142, 619–624
[3] K. H. Jung. *Contrast Media Mol. Imaging*. **2018**, 01, 3727109

O100

Features of changes in the properties of microparticles of elemental boron in the process of fine grinding

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A potentially new form of therapeutic drug for BNCT in the form of elemental boron nanoparticles was obtained using fine milling. The process of fine grinding of materials is one of the most common and widely used methods of obtaining nanomaterials.

The paper presents the results of studies of fine comminution of boron microparticles under cavitation conditions. As the size of boron particles decreased, the following peculiarity was noted: the critical size of nanoparticles was reached at which allotropic crystal modification was observed to change according to X-ray phase analysis. Along with the change in the crystal structure in boron nanoparticles, by methods of infrared spectroscopy, X-ray photoelectron spectroscopy, it was shown how the properties of their surface change with decreasing particle size: the content of hydride and oxidized forms of boron decreases, in nanoparticles sized from 5 to 20 nm a complete disappearance of oxidized layers in the surface is observed.

The time of complete oxidation of boron particles depending on their size was evaluated: with decreasing size the time of complete oxidation of boron to boric acid increases, which is associated with a change in their allotropic modification - a more oxidation-resistant crystalline structure is formed.

As the size of boron particles decreases, their aggregation over time increases, we have studied the sedimentation stability of boron nanoparticles in various high molecular weight stabilizing systems. Detailed studies and conclusions will be presented during the report.

Keywords:

elemental boron, nanoparticles, cavitation, fine crushing, neutron irradiation, accelerator-based neutron source.

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Inorganic, small and anionic molecule uptake targets metabolic heterogeneity of glioma stem cells

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The anionic cobaltabis(dicarbollide) [3,3'-Co(1,2-$C_2B_9H_{11})_2]^-$, [*o*-COSAN]$^-$, in which the Co^{3+} ion is a common vertex between two $[C_2B_9H_{11}]^{2-}$ clusters, is the most studied icosahedral metallacarborane. [*o*-COSAN]$^-$ possesses the capacity to produce hydrogen and dihydrogen bonds (C_c-H···O and C_c-H···H-B or N-H···H-B, respectively), which have been proven to participate in their self-assembling. The H^+ and Na^+ salts of [*o*-COSAN]$^-$ forms micelles and vesicles in aqueous solution.[1] Boranes are essentially nontoxic due to their inertness to biochemical reactions. In addition, the protonated and sodium salts of [*o*-COSAN]$^-$ possess the ability to readily cross biological membranes[2] not being immediately cytotoxic, but cytostatic over long term, and cells recover following its removal.[3] These abilities make the $[Na{\cdot}2.5H_2O][3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]$, Na[*o*-COSAN], to be considered as a candidate for the anti-cancer treatment Boron Neutron Capture Therapy (BNCT). BNCT is based on the potential of ^{10}B atoms to produce α particles that cross tissues and weakens tumorous cells without damaging the surrounding healthy tissues, after being irradiated with low energy thermal neutrons.[4]

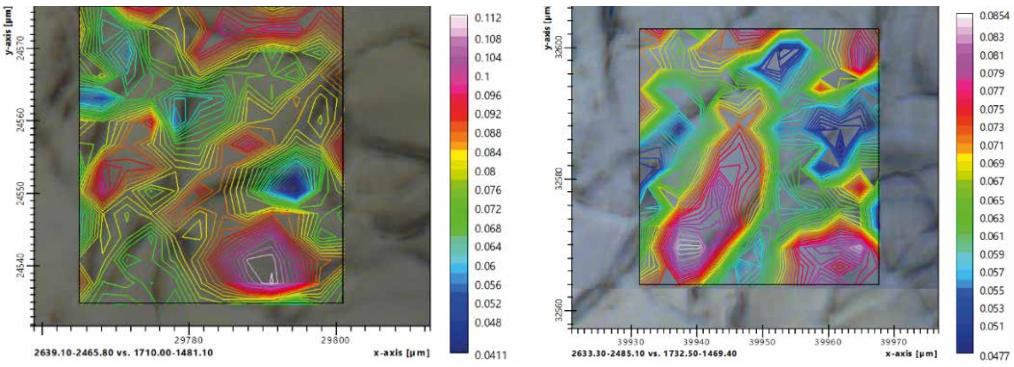

Figure 1.- Mappings of integrated Na[*o*-COSAN] FTIR band (2460-2620 cm^{-1}) into GIC7 cells after being incubated with 2mM Na[*o*-COSAN] for 5 hours.

Following our studies, the uptake of Na[*o*-COSAN] by two different phenotypes of glioma initiating cells (GICs), mesenchymal (PG88) and proneural (GIC7) GICs, using Synchrotron Radiation-FTIR microscopy facilities at the MIRAS Beamline in ALBA synchrotron has been studied. Taking advantage that Na[*o*-COSAN]

displays a strong and characteristic ν(B-H) frequency in the mid-infrared range 2.600-2.500 cm^{-1} in which no other frequencies of organic compounds appear, we have studied the interactions of Na[*o*-COSAN] with cell's biomolecules (DNA, proteins and liposomes). These studies allowed us to locate [*o*-COSAN]$^-$ into the cells. Cell mapping was acquired (Figure 1) and spectroscopic data were obtained from bands in the regions that correspond to the DNA, proteins, and lipids to determine into the cancer cells and in each region of the spectra the [*o*-COSAN]$^-$-biomolecules interactions after Na[*o*-COSAN] uptake. These data suggest that Na[*o*-COSAN] is sandwiched between DNA strings,[5] and is compatible with modifications in protein structure and lipid saturation. In conclusion, we show evidences that at low doses, [*o*-COSAN] translocates GIC cells' membranes and then, it alters the physiology of the cells. Cycle cell analysis on GICs cells as well as cell viability (EC_{50}) tests were also performed. Such results indicate that Na[*o*-COSAN] may be a promising agent to be tested in BNCT treatment of glioblastoma cancer in the future.

Keywords:

Boron neutron capture therapy, Glioblastoma, Cobaltabis(dicarbollide), SR-FTIR, intermolecular interactions, biomolecule's modification.

References:

[1] a) P. Bauduin, S. Prevost, P. Farras, F. Teixidor, O. Diat, and T. Zemb, *Angew. Chem. Int. Ed.*, **2011**, 50, 5298-5300. b) D. C. Malaspina, C. Viñas, F. Teixidor, J. Faraudo. *Angew. Chem. Int. Ed.* **2020**, 59, 3088-3092. c) M. Uchman, V. Dordovic, Z. Tosner, P. Matejicek. *Angew. Chem. Int. Ed.* 54 (2015) 14113.

[2] a) C. Verdiá-Báguena, A. Alcaraz, V. M. Aguilella, A. M. Cioran, S. Tachikawa, H. Nakamura, F. Teixidor and C. Viñas. *Chem. Commun*. **2014**, 50, 6700-6703. b) M. Tarrés, E. Canetta, C. Viñas, F. Teixidor, A.J. Harwood. *Chem. Commun*. **2014**, 50, 3370.

[3] M. Tarrés, E. Canetta, E. Paul, J. Forbes, K. Azzouni, C. Viñas, F. Teixidor and A. J. Harwood. *Sci. Rep*. **2015**, 5, 7804.

[4] a) Neutron Capture Therapy Principles and Applications. Eds. W. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa. Springer 2012. b) R. F. Barth, M. G. H. Vicente, O. K. Harling, W. S. Kiger, K. J. Riley, P. J. Binns, F. M. Wagner, M. Suzuki, T. Aihara, I. Kato, S. Kawabata. Radiat Oncol J. 2012, 7, 146.

[5] I. Fuentes, T. García-Mendiola, S. Sato, M. Pita, H. Nakamura, E. Lorenzo, F. Teixidor, F. Marques, C. Viñas, *Chem. Eur. J*. **2018**, 24, 17239–17254.

Development of new small molecule drugs for Boron Neutron Capture Therapy

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Despite obvious benefits the adoption of Boron Neutron Capture Therapy (BNCT) in the clinic has been slow because of its reliance on nuclear reactors as a source of neutrons and challenges using the existing BNCT drug, boronophenylalanine (BPA). To overcome these obstacles several companies have developed accelerator-based neutron beam systems and some are investigating alternative drugs to BPA. BPA has been approved for BNCT in Japan so we know that it works but certain limitations mean that there is room for improvement. One of these limitations includes its low solubility, which means that high volumes of the solution need to be administered via the i.v. route, limiting the dose that can be given. It is known that for successful BNCT at least 20 μg of ^{10}B needs to be delivered per gram of tumor whereby a tumor to normal ratio (T:N) for boron of 3:1 is typically achieved. If the amount of boron delivered could be increased and the T:N ratio improved we would expect to see even better BNCT outcomes than we see today.

We aim to improve the cellular ^{10}B uptake by developing non-natural boronated amino acids and dipeptides with better solubility than BPA, thus increasing the delivered boron dose. These boronated amino acids or dipeptides are designed based on structural activity relationship (SAR) for known LAT1 substrates. The non-natural amino acids and peptides are synthesized via either a novel synthetic route or by standard peptide coupling, respectively.

We synthesized several borylated non-natural amino acids and showed that they have better solubility than BPA; >100 mg/ml vs. 1.6 mg/mL for BPA and, unlike BPA, some do not require fructose for improved water solubility. In vitro functional studies using the LAT1 expressing FaDu cell line (human hypo-pharyngeal carcinoma) showed one new compound, i.e. BTS, had an 80% higher uptake compared to BPA when tested at equal concentrations (see Figure 1). The best boron uptake observed was 1857 ng of boron per mg of tumor protein versus 1073 ng per mg for BPA. This new compound was also retained longer in cells. Further tests suggested that this compound has a higher V_{max} (rate of uptake) for LAT1 compared to BPA. LAT1 specificity was confirmed by a competition assay with phenylalanine and an inhibition assay with JPH203 ((O-[(5-amino-2-phenyl-7-benzoxazolyl)methyl]-3,5-dichloro-L-tyrosine dihydrochloride) and BCH (2-amino-2-norbornanecarboxylic acid), two known LAT1 inhibitors.

In biodistribution studies, using CB17-SCID mice subcutaneously implanted with FaDu xenografts, our lead compounds demonstrated a dose-dependent tumor uptake and were able to deliver up to 66 mg boron per gram of tumor cells compared with 26 mg per gram for BPA. Remarkably, we also observed a more rapid blood clearance for one of these compounds when compared to BPA and, due to this, we were able to achieve a tumor:blood ratio as high as 30:1 compared with 7:1 for BPA.

We are also investigating boron carrying dipeptides and have shown that they are also substrates for LAT1, however, due to their size, they may also be engaging the peptide transporter PEPT-1 that has been reported to be

overexpressed in certain tumors. If this is the case we may see improved boron delivery as 2 transporters are being used.

These new boron carriers have the potential to improve BNCT treatments, bringing a much needed option to patients with head and neck cancer or glioblastoma who have often failed to respond to other standard therapies. This will help speed up the development of BNCT, Our aim is to begin clinical trials with these new molecules in the US and Europe within the next 2 to 3 years.

Keywords:
BNCT, boron uptake, boronated amino acid, BTS, BPA, head and neck cancer

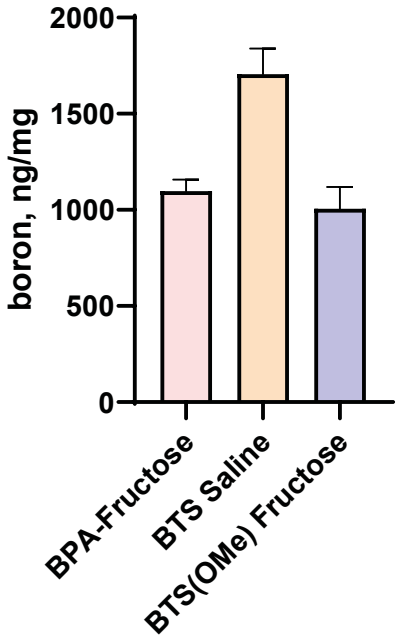

Figure 1. *Boron uptake at 2 hr using FaDu cells*

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Target selection and development of antibody boron conjugates for boron neutron capture therapy of head and neck cancer

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The most widely used drug for boron neutron capture therapy (BNCT) is boronophenylalanine (BPA). It is approved for BNCT in Japan and initial response rates are very high. However, BPA does have limitations as it carries only one boron atom per molecule and it is not directly targeted, relying instead on passive uptake through LAT1. Although LAT1 is upregulated in some tumor types expression can be variable, with some tumors having high levels and some having low or no expression. This can lead to inconsistent boron delivery and may explain why many patients treated with BNCT relapse, despite a promising initial response. Thus, identification of new boron delivery agents is needed to address the shortcomings associated with BPA in both targeting and boron payload delivery. New targeted boron drugs should facilitate wider adoption of BNCT as a key cancer treatment option. Fundamental to the success of improving BNCT with BPA is the selection of a more specific high content boron delivery vehicle such as an antibody. Antibody drug conjugates have been successful in the treatment of several cancers due to their relative specificity for cancer cells that have high target expression. To increase target specificity and boron loading we are exploring well known ADC targets with the aim of developing antibody boron conjugates (ABCs) combined with novel boron enriched linkers for BNCT.

In the present study we use immunohistochemical (IHC) analysis with commercially available IHC reagents to compare expression of LAT1 with EGFR, and two other biomarkers in head and neck cancer (HNC) (BM3 and BM4). We ranked the target expression in the HNC samples using a combination of percentage of tumor area that was positive and signal strength. The premise being that for BNCT, where you need biological targeting of as many cells as possible, homogenous expression, even at moderate levels, is better than high expression if it is only limited to small parts of the tumor. Using a cut off of 80% and 50% expression across each tumor biopsy we found that LAT1 had high levels of expression in only a small subset of biopsies whereas other targets evaluated had more consistent homogenous expression in a greater percentage of cases. This may make them better targets for BNCT by allowing boron to be delivered to more tumor cells in a greater number of patients during treatment. Preliminary results in 32 HNC samples showed that only 28% had greater than 80% of the tumor positive for LAT1 whereas EGFR was expressed in over 80% of tumor cells in 84% of patients. Higher and more consistent expression was also observed for BM3 and BM4 indicating once again that LAT1 may not be the best choice for tumor targeting in BNCT.

First generation ABCs, with hundreds of boron atoms per antibody, were produced using proprietary boron enriched linkers (BELs) conjugated to antibodies targeting EGFR. ABCs generated had good biochemical properties and were able to bind to EGFR without any loss of affinity. In addition, they were able to internalize, delivering increasing amounts of boron with increasing antibody-boron load and increasing target expression on cells.

In conclusion, we have shown that EGFR, BM3 and BM4 may be better cancer targets than LAT1 for treating HNC by BNCT due to higher homogenous expression in more patient tumor samples. ABCs to these targets have

the great potential to become the next generation of boron delivery agents for BNCT improving on BPA. This could dramatically increase patient treatment options and outcomes, not just for HNC but also for many other cancers.

Keywords:

Boron neutron capture therapy (BNCT), cancer biomarkers, antibodies, antibody boron conjugates, immunohistochemistry (IHC), LAT1, EGFR

Chemistry and pharmacology

Poster

Synthesis of new Sulfonamide-Functionalized Carborane: Bifunctional Agent for Coupling BNCT with Inhibition of CAIX

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Carbonic Anhydrase (CA), an important family of metalloenzymes that catalyse reaction between water and carbon dioxide to give bicarbonate and a proton, has been well investigated because of its influence on the microenvironment of solid tumour. It is known that this latter is hypoxic and more acidic than normal. CA-IX was identified to be overexpressed in many tumours, including mesothelioma and breast cancer and it plays a role in producing and maintaining an intracellular pH favourable to tumour cell growth. It has been widely reported that sulfonamide-functionalized molecules are able to block the activity of CA-IX. In a previous work, Brynda *et al* proposed a sulfonamide-functionalized carborane **1a** (CA-SF) as CA-IX inhibitor (figure 1, left).[1]

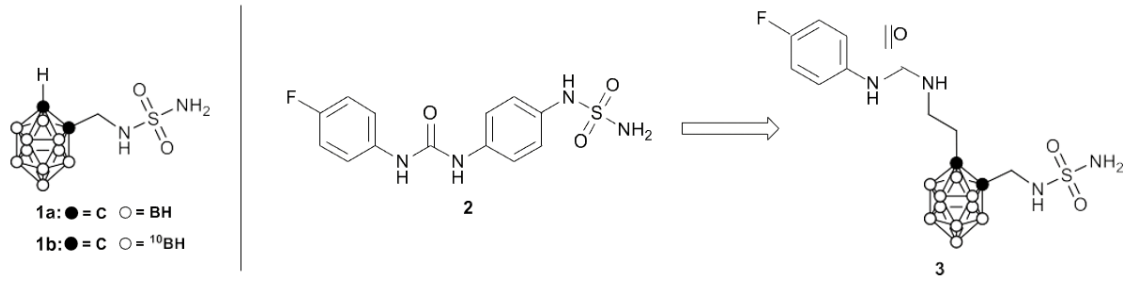

*Figure 1 On the left: structure of sulfonamide-functionalized carborane (CA-SF) reported in our work. On the right: structures of ureido sulfamidic compound **2** and of the bifunctional agent **3**, purpose of this research.*

The coupling of the carborane cage with sulfamido group allows this compound as a bifunctional agent able to combine of CA-IX inhibition and boron delivery agent for Boron Neutron Capture Therapy (BNCT) to be exploited. In our work was demonstrated that ^{10}B-CA-SF **1b** (figure 1, left) displays a synergic toxic effect on cells overexpressing CA-IX enzyme with a very limited mesothelioma cells re-growth after neutron irradiation.[2] In order to enhance the selectivity of ^{10}B- CA-SF our group is moving on the design of a sulfonamide-functionalized carborane **3** inspired to compound **2**, a selective inhibitor for the tumour associated CA-IX that is currently in phase I/II clinical trials (figure 1, right).[3] Nowadays, many progresses had been done regarding the treatment of various tumours and this new bifunctional agent could be a promising improvement for this very important field.

Keywords:
Carbonic Anhydrase, carborane, BNCT, sulfonamide, bifunctional agent.

References:

[1] J. Brynda, P. Mader, V. Šícha, M. Fábry, K. Poncová, M. Bakardiev, B. Grüner, P. Cígler, P. Řezáčová *Angew. Chem. Int. Ed.* 2013, **52**, 13760.
[2] D. Alberti, A. Michelotti, A. Lanfranco, N. Protti, S. Altieri, A. Deagostino, S. Geninatti Crich *Sci. Rep.* 2020, **10**, 19274. [3] A. Angeli, F. Carta, A. Nocentini, J.Winum, R. Zalubovskis, A. Akdemir, V. Onnis, W. M. Eldehna, C. Capasso, G. De Simone, S. M. Monti, S. Carradori, W. A. Donald, S. Dedhar, C.T. Supuran *Metabolites* 2020, **10**, 412.

Improvement of therapeutic effect of D-4-boronophenylalanine by poly(vinyl alcohol)

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L-4-Boronophenylalanine (L-BPA) is the most clinically studied boron drug in boron neutron capture therapy (BNCT). L-BPA has a phenylalanine-like structure and is taken up by many cancer cells via the amino acid exchange transporter LAT1. However, with the decrease in extracellular L-BPA concentration, intracellular L-BPA is exchanged with an extracellular amino acid such as tyrosine, making it difficult to maintain a high intratumor boron concentration in the long term [1]. In this regard, we recently reported that poly(vinyl alcohol) (PVA) can form PVA-L-BPA complexes with multiple BPA molecules via boronate esters, and PVA-L-BPA was internalized into the cells through LAT1-mediated endocytosis, suppressing the extracellular efflux of L-BPA and increasing cellular uptake of L-BPA [2]. PVA-L-BPA importantly accomplished significantly enhanced BNCT effect in subcutaneous tumor models.

Meanwhile, L-phenylalanine is recognized not only by LAT1 but also by LAT2 and $ATB^{0,+}$, whereas D-phenylalanine is known to have high selectivity for LAT1 [3,4,5]. Thus, it can be expected that conjugation of D-BPA, a stereoisomer of L-BPA, with PVA may result in the higher tumor specificity than L-BPA. In this study, we investigated the effect of this stereoisomerism on the pharmacokinetics of PVA-BPA,

In the *in vitro* study, we evaluated the cellular uptake of sorbitol-L/D-BPA and PVA-L/D-BPA and the effect of the LAT1 inhibitor on the uptake in LAT1-positive cancer cells by using inductively coupled plasma mass spectrometry. The uptake of sorbitol-D-BPA was about 50% lower than that of sorbitol-L-BPA, but the uptake of D-BPA was increased by about two times with PVA. The uptake of all samples was significantly decreased by the LAT1 inhibitor, and the inhibitory effect on D-BPA was considerably higher than that on L-BPA. Also, when cells were contacted with each sample for 3 h and then cultured in sample-free medium for 30 min to evaluate intracellular retention, the samples using D-BPA showed more than two fold higher intracellular retention than that of L-BPA. In biodistribution study with subcutaneous tumor models, the L-BPA group accumulated in the tumor within 1 h, and PVA-L-BPA showed long-term tumor retention 1-6 h after intravenous injection. On the other hand, sorbitol-D-BPA showed little accumulation, while PVA-D-BPA exhibited higher accumulation than PVA-L-BPA at 6-12 h after administration. Consequently, PVA-D-BPA showed high antitumor effect comparable to PVA-L-BPA in BNCT. PVA-D-BPA may be a promising drug delivery system targeting LAT1.

Keywords:
p-boronophenylalanine (BPA), LAT1, drug delivery system, polymer, stereoisomerism of amino acid.

References:

[1] A. Wittig, et al., Mechanisms of transport of *p*-borono-phenylalanine through the cell membrane in vitro, ***Radiat. Res.*** 153 (2) (2000) 173-180.

[2] T. Nomoto, et al., Poly(vinyl alcohol boosting therapeutic potential of *p*-boronophenylalanine in neutron capture therapy by modulating metabolism, ***Sci. Adv.*** 6 (4) (2020) eaaz1722.

[3] P. Wangthai, et al., Boronophenylalanine, a boron delivery agent for boron neutron capture therapy, is transported by $ATB^{0,+}$, LAT1 and LAT2. ***Cancer Sci.*** 106 (3) (2015) 279-286.

[4] O. Yanagida, et al., Human L-type amino acid transporter 1 (LAT1): characterization of function and expression in tumor cell lines. ***Biochimica et Biophysica Acta.*** 1514 (2) (2001) 291-302.

[5] H. Segawa, et al., Identification and Functional Characterization of Na^+- independent Neutral Amino Acid Transporter with Broad Substrate Selectivity. ***J. Bio. Chem.*** 274 (28) (1999) 19745-19751.

The loading of Cobaltabisdicarbollide (COSAN) into the Apoferritin cavity increases its selective uptake by breast cancer cells: a key feature for Boron Neutron Capture Therapy applications.

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The development of highly specific, efficient, non-toxic and biodegradable boron delivery systems is a challenging issue to fully exploit the high potentiality of BNCT. The use of proteins is a promising option for achieving this goal. Indeed, these macro-molecules are ideal for the development of drug-delivery platforms, thanks to their biocompatibility and, in many cases, the overexpression of their receptors/transporters on cancer cells. Ferritin is a nanocage of 12 nm composed by 24 subunits of heavy (H)- and/or light (L)-chain peptides to form a cage architecture with an interior cavity of 8 nm. Ferritin is the main iron cellular storage molecule in the body, and it has also been extensively studied for the delivery of biologically active molecules or metal ions, incapsulated in its internal cavity, for many biomedical applications.[1,2] In this study we propose the use of apoferritin for the selective delivery of cobaltabis(dicarbollide) (COSAN), exploiting "the innate" targeting ability of this protein cage to tumors. The use of COSAN [3] has many advantages: 1) high boron content (18 boron atoms/molecule), 2) its ability to cross biological membranes, and 3) no apparent effect on the cell viability.

Using an efficient entrapping method, based on the breaking down of the apoferritin nanoarchitecture in an acidic environment and restoring it by retuning the pH to 7.4, it was possible to entrap in the inner cavity 6 COSAN molecules corresponding to 108 boron atoms. Then the boron uptake by a human breast cancer cell line (MCF7) was measured by ICP-MS and compared with those obtained by incubating COSAN alone at the same concentrations.

The amount of boron taken up by cells after incubation with APOCOSAN was of ca 35 ppm compared to ca. 10 ppm internalised with COSAN alone. We can conclude that apoferritin is an efficient and specific platform for the delivery of boron containing compounds; moreover the protein cavity can host also imaging agents for biodistribution monitoring. BNCT will be performed on cells incubated with COSAN and APOCOSAN in order to evaluate the cytotoxic effect reached after neutron irradiation.

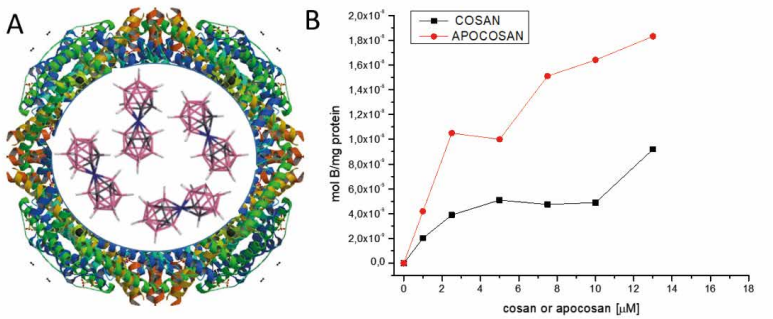

Figure 1. *a) Schematic representation of apoferritin loaded with COSAN; b) Boron uptake by MCF7 cancer cells after 6h incubation with COSAN and APOCOSAN at different concentrations, measured by ICP-MS.*

Keywords:
COSAN, apoferritin, breast cancer, nanoparticles

References:

[1] Ruggiero MR et al Inorganics, 7, 33, 2019;
[2] Bitonto V, et al J Control Release. 319, 300, 2019;
[3] Fuentes I et al Chem. Eur. J, 24, 17239, 2018.

Efficient Synthesis of [18F]FBPA based on “F-Minus Method”

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18FBPA-PETは、がんBPA　　BNCT医療のコンパニオン診断モダリティーとして広く認識され、そのプローブ分子である18FBPAの効果的な合成法の開発が求められている。

18FBPA-PETは、がんBPA　BNCTに必須のコンパニオン診断モダリティーとして広く認識され、BPAと同等の薬物動態を示すプローブ分子、18FBPAの効果的な合成法の開発が求められている。

BPAと同等の薬物動態を示す18FBPAは、がんBPA BNCT

18FBPA-PETは、がんBPA BNCT治療のコンパニオン診断モダリティーとして広く認識され、BPAと同等の薬物動態を示すプローブ分子である18FBPAの効果的な合成法の開発が求められている。単語数４３

18FBPA-PET is widely recognized as a companion diagnostic modality for the treatment of cancer BPA BNCT, and there is a need for the development of an effective synthetic method for 18FBPA, which is a probe molecule showing pharmacokinetics equivalent to that of BPA.

[18F]FBPAは現在、BPAに[18F]-CH3COOF (acetic hypofluorus anhydride) から生じるF+ イオンを反応させる芳香族求電子置換反応、所謂“F-プラス法”により合成されている。この合成方法は保護基のないBPAを単工程で[18F]で標識化できる便利な方法であるが、得られる18FBPAの比放射能が低く改善が必要とされている。単語数69

[18F] FBPA is currently synthesized by the so-called “F-plus method”, which is an aromatic electrophilic substitution reaction in which BPA is allowed to react with F + ion generated from [18F] -CH3COOF (acetic hypofluorus anhydride). This synthetic method is a convenient method that allows BPA without protecting groups to be labeled with [18F] in a single step, but the specific activity of the obtained 18FBPA is low and improvement is needed.

我々は、現行の“F-プラス法”に替わり、加速器から得られる[^{18}F]-HFより調整した[^{18}F]-KFなどのフッ化物をフッ素化剤に用いる“F-マイナス法”による[^{18}F]FBPAの新規合成法に着目した。

ウ素中性子捕捉療法（BNCT）用ホウ素薬剤として研究されてきたBPA　[国際一般名（INN）：ボロファラン（^{10}B）]を有効成分とする薬剤であるステボロニンは、2020年3月に日本で医薬品として規制当局である医薬品医療機器総合機構（PMDA）から新薬として承認され、頭頸部がんを対象としたBNCTの実医療に用いられている。現在、BPAの薬物動態を確認する方法として、PET核種である^{18}Fで放射性標識された4-ボロノ-2-　[18F]フルオロ-L-フェニルアラニン（[^{18}F]FBPA）を使用したPET技術がある。FBPA　PET診断とBPA-BNCTを組み合わせることで、患者ごとに最適な投与方法や照射タイミングを設定できる可能性がある。[^{18}F]FBPAは、現在、石渡らにより開発された“F-プラス法”により合成されている。加速器から得られる[^{18}F]-F_2より調製した[^{18}F]-CH_3COOF　(acetic hypofluorus anhydride) をフッ素化剤に用い、BPAから単工程の反応で^{18}FBPAを得る優れた合成法であるが、^{18}FBPAの比放射能が低く、より効率的な合成法の開発が求められている。

我々は、現行の“F-プラス法”に替わり、加速器から得られる[^{18}F]-HFより調整した[^{18}F]-KFなどのフッ化物をフッ素化剤に用いる“F-マイナス法”による[^{18}F]FBPAの新規合成法に着目した。この方法により比放射能の高い[^{18}F]FBPAを高収率で得られることが期待される。反応収率を指標として、コールド条件による検討を重ね、最終の合成経路を選択した。即ち、2位及び4位が、それぞれピナコールボレート及び臭素に置換されたL-フェニルアラニンエステル誘導体を前駆体に用い、これに^{18}F-フッ素化、ボロン酸残基の構築、脱保護を行うものである（図1）。

ホット条件下での検討も実施し、約20%の放射化学的収率で得られた[^{18}F]FBPAの比放射能は高く、光学純度は＞98% e.e.であった。現在、さらなる反応収率の向上を目指して自動合成装置による最適化を継続検討している。

Evaluation of gadolinium neutron-capture therapy as a new therapeutic option for bulky tumors

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Neutron-capture therapy using nonradioactive ^{157}Gd (Gd-NCT) is currently under development as a potential radiation therapy option for cancer. Gd-NCT with ^{157}Gd has several potential advantages over boron (^{10}B) neutron capture therapy (BNCT). γ-rays emitted by the ^{157}Gd (n, γ) ^{158}Gd reaction offer deep tissue penetration (100 μm), expected to provide tumor-killing efficacy within bulky tumors such as head and neck cancers. We have previously developed gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs) for controlled Gd delivery in Gd-NCT. These nanoparticles are composed of Gd-diethylenetriaminepentaacetic acid (Gd-DTPA, an MRI contrast agent), and chitosan (a naturally abundant biodegradable polysaccharide with good biocompatibility and bioadhesive characteristics). We here investigate *in vivo* the antitumor effects of NCT for bulky tumors by intratumoral injection of these nanoparticles.

Gd-nanoCPs were prepared using a previously developed w/o emulsion droplet coalescence technique [1]. Mean particle size and zeta potential of the resultant Gd-nanoCPs were measured by Zetasizer. Gd content of the Gd-nanoCPs was determined by ICP-AES. Male SCC-VII tumor-bearing C3H/HeN mice were divided into an NCT group and a HOT control group. Prior to treatment, the NCT group was subdivided into a small tumor volume (< 500 mm^3) group, and a large tumor volume (> 500 mm^3) group. Mice were intratumorally injected twice with Gd-nanoCPs incorporating 1.2 mg/kg/injection of natural Gd. Tumors in left hind legs were exposed to thermal neutron irradiation at the Institute for Integrated Radiation and Nuclear Science, Kyoto University. Tumor volumes were determined by measuring two bisecting tumor diameters with a slide caliper. Tumor-growth suppression was assessed by the ratio of tumor volumes before and after neutron irradiation.

Mean particle diameter, Gd content, and zeta potential of the Gd-nanoCP were 165 nm, 22%, and +23 mV, respectively. Before injection, Gd-nanoCPs were concentrated to 6000 μg Gd/mL with a centrifuge. In the NCT trial, eight hours after the last administration, thermal neutron irradiation was applied to mouse tumors. The NCT group significantly suppressed tumor growth relative to that observed in the HOT control group. Decreases in tumor volume were similar to those observed in our previous study using a subcutaneously trans-planted melanoma-bearing mouse model [1]. Tumor volume growth in the large tumor volume group was slower than that in the small tumor volume group, indicating that Gd-nanoCPs displayed potent tumor tissue affinity and reduced tumor tissue volume over a wide area while they did not eliminate tumors. Gd-NCT using Gd-nanoCPs could thus be a promising therapeutic option to shrink bulky tumors.

Keywords:
Gadolinium neutron capture therapy, head and neck cancer, nanoparticle

References:

[1] H. Ichikawa et al., Appl. Radiat. Isot., 88, 109-113 (2014).

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Novel Boronated Monocarbonyl Analogues of Curcumin (BMAC): A new approach to fight Alzheimer's disease

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AD is a progressive neurodegenerative disorder characterized by cognitive decline, irreversible memory loss, disorientation and language impairment. One of the pathological hallmarks is the aggregation of Aβ peptide and its accumulation in the human brain has an important role in the etiology of AD. Although there are several isoforms of Aβ species, Aβ40 and Aβ42 are the most abundant and Aβ42 is more aggregation-prone. During aggregation, Aβ monomers undergo conformational changes to form misfolded intermediates that subsequently assemble into β-sheets enriched conformers, including oligomers, protofibrils, and fibrils. In particular, soluble oligomeric/prefibrillar Aβ have been shown to be potent neurotoxins. Therefore, inhibiting or disrupting the Aβ aggregation process represents a promising therapeutic strategy for the prevention and treatment of AD [1]. Moreover, Curcumin has become a research focus due to its effect of anti-Aβ fibrils as highly beneficial in the treatment of AD. Some doubts about Curcumin's effectiveness have recently been raised, and these are mainly associated to its instability. The reactivity of the β-diketone moiety is one of the causes of this drawback. For these reasons many efforts have been devoted to the synthesis of Curcumin analogues that can improve molecular stability such as mono carboranyl 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 (BMAC, 6c) (Fig.1) in which one aromatic ring is replaced with an ortho-carborane and the other is a dihydroxyphenyl group. The reported efficacy of the boronated Curcumin analogues in reducing lysozyme fibril formation, and the presence of boron atoms in the carborane cage will drive us to evaluate the feasibility of using BNCT as a radiative boost to enhance fibril disaggregation [2].

To evaluate the inhibition of Aβ peptide aggregation, Aβ42 peptide (0.05 mM) has been incubated in physiological condition (37°C, PBS pH 7.4), under stirring, with or without 150μM BMAC 6c compound for 72h, in order to have Aβ aggregates in protofibrillar and fibrillar state [1,3]. Then, the samples were stained with Congo Red, one of the compound commonly used for detecting Aβ aggregates. When the Congo Red binds the protein, a bathochromic shift from the original absorbance peak is observed in the UV-VIS spectrum [4]. Other samples prepared as described above have been analyzed directly by spectrofluorometer and emission spectra have been studied: a shift to the red in the emission peak is observed when the protein is in the unfolded state [5]. Moreover, not only the inhibition of fibrils formation but also the disaggregation ability of BMAC 6c was evaluated incubating the compound for other 72h after fibril formation. These preliminary studies show the inhibitory effect of BMAC 6c on aggregation study and its effectiveness on disaggregation studies upon 150μM BMAC 6c incubation. It has been found a 35% inhibition and 74% of disaggregation power. At the end of disaggregation study, the amount of boron present in the Aβ aggregates was determined by ICP-MS and it was ca. $63x10^3$ ppm, a concentration that allow us to move to the next step that involves the irradiation of the sample with neutrons, to induce a complete disaggregation. Further tests will be carry out:

electrophoretic analysis and fluorescence microscopy for the evaluation of the fibrils size and BMAC-fibrils interactions and cytotoxicity assays on immortalized astrocytes or other cell models in order to evaluate both Aβ aggregates and neutron irradiation toxicity.

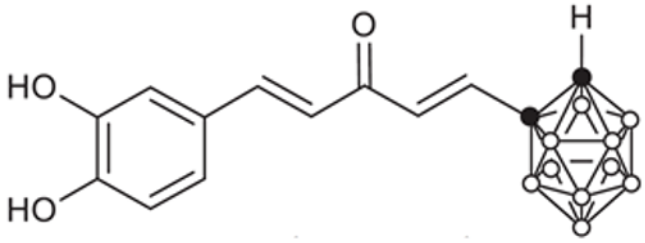

Figure 1. BMAC 6c

Keywords:
Curcumin, MAC (Monocarbonyl analogues), BMAC (Boronated Monocarbonyl Analogues), Alzheimer's disease, Carboranes

References:

[1] A. Thapa et al., ACS Chem Neurosci, 7(1):56-68, 2016
[2] E. Azzi et al., Bioorg Chem. 93:103324, 2019.
[3] C.S. Goldsbury et al., J. Struct. Biol. 130, 217-231, 2000.
[4] W.E. Klunk et al., Methods Enzymol 309, 285-305, 1999.
[5] C.A. Royer, Chem Rev. 106, 1769-1784, 2006

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Boron oxide/human albumin nanoparticles as potential boron carrier for BNCT: initial pilot study to determine the concentration of B in the solution using the ICP-OES technique

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Introduction: Multiple international efforts are aimed at the development of new boron carriers for Boron Neutron Capture Therapy (BNCT) with a greater therapeutic potential than the existing compounds. The development of new boron carriers seeks to maximize the total boron content in the tumor and enhance selective uptake in different tumor populations of a heterogeneous tumor. Considering the need to obtain compounds enriched in ^{10}B that are compatible with biological systems, hybrid nanoparticles (HNPs) composed of B and Human Serum Albumin (HSA) were prepared. The boron concentration of solutions of HNPs was measured by means of the ICP-OES technique. **Aim:** to perform an initial pilot study to determine the concentration of B using the ICP-OES technique of solutions of HNPs with or without HSA as potential boron carrier compounds for BNCT.

Materials and methods: the HNPs were synthesized at the National University of Quilmes from boron oxide and oleic acid and subsequently coated with HSA to confer biocompatibility. Characterization was carried out using DLS, TEM, FTIR techniques. Two HNPs solutions, with or without HSA, were processed by nitric acid digestion at 100ºC for 2 h and sonicated at 60ºC for 1 h for boron measurement by atomic emission spectroscopy (ICP-OES) at the Radiobiology Department-CNEA. For the quantitative measurement of the [B] in the samples, the atomic emission spectra of the lines 208.889 and 249.677 nm were analyzed.

Results: The HSA-coated HNPs exhibited a core/shell type spherical nanometric structure, with an average hydrodynamic diameter of 40 nm. Furthermore, the presence of the protein coating was confirmed. On the other hand, NPs without HSA show an average hydrodynamic size of 20 nm. The mean B concentration of the HNPs, with or without HSA, were 199 ± 209 ppm (n=3) and 12068 ± 3590 ppm (n=3), respectively. **Conclusion:** these pilot results would demonstrate that the B concentration of the solution of borated nanoparticles without coating of HSA was ≥ 10000 ppm, similar to the solutions of other borated compounds employed successfully with different administration protocols in biodistribution assays in animal models (ex: BPA, BSH, BA, GB-10). Therefore, the HNPs without HSA would be a potential boron carrier for *in vitro* and *in vivo* BNCT studies. On the other hand, the low boron concentration values for the solution of the HNPs with human serum albumin warrant future B measurement tests with different digestion protocols.

Keywords:
boron distribution; BNCT; nanoparticles.

Evaluation of novel boron cluster conjugated PEG derivative for BNCT

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INTRODUCTION:

There has been a growing interest in Boron Neutron Capture Therapy (BNCT) because they are expected to be next generation therapy in minimally invasive cancer treatment. And BNCT using *p*-boronophenylalanine (BPA) was started as the medical treatment in Japan, 2020. However, large doses of BPA are required to achieve a favorable therapeutic effect and ^{10}B retention in tumor cells is limited in time, leading to the need for continuous BPA infusion even during neutron irradiation.

To address the issue of boron accumulation and retention in tumor tissue, we developed boron cluster conjugated PEG derivative (named BAMP), a novel boron compound [1, 2]. Therefore, we report the results of a non-clinical study on whether BAMP can be applied to BNCT as effective boron drug.

MATERIALS AND METHODS:

1. Cytotoxicity of BAMP

The cytotoxicity of BAMP was evaluated by WST assay using CT26 (mouse colon carcinoma cell) and V79 374A (Chinese hamster lung fibroblast). Each cell precultured with CO_2 incubator for 24 hours and, were exposure to BAMP with CO_2 incubator for 24 hours. After adding CCK-8 solution with CO_2 incubator for two hours, it was measured absorbance (450nm) and calculated a cell survival rate.

2. Biodistribution of BAMP in tumor-bearing mice

The tumor-bearing mice were prepared by grafting 5 x 10^6 of mouse colon carcinoma cells (CT26) to the right thigh of female BALB/cA mice (4 weeks old, weighing 16-20 g) to have a tumor diameter of 6-8 mm. About 10 days after, BAMP was administered by tail vein injection. At selected time intervals after administration, mice were anesthetized, bled via the retro-orbital sinus, killed by cervical dislocation and dissected. And after, each tissue was excised and their ^{10}B content was measured by ICP-AES.

3. Therapeutic effect of BNCT using BAMP in tumor-bearing mice

The tumor-bearing mice were prepared similarly to the experiment of biodistribution, and each sample was administered by tail vein injection before irradiation. And the irradiation was performed with thermal neutrons with a flux of 5.2 x 10^{12} neutrons/cm^2 over 1 hour. The tumor diameter was measured over time after the irradiation until Day 24, and the tumor size was calculated using the general formula [3].

RESULTS AND CONCLUSION:

Our results demonstrate that BAMP can be applied to BNCT as effective boron drug. The results of *in vitro* suggest that BAMP is safe even at high concentrations. And, when BAMP was administered, it was rapidly eliminated from normal tissue including liver and kidney but remained in the tumor to 48 hours after. Also, in the experiment of thermal neutron irradiation using tumor-bearing mice, BAMP significantly suppressed the tumor growth as compared to other control groups without remarkable side effect (e.g. weight loss)

We conclude that BAMP indicated its excellent candidate drug potential for BNCT.

Keywords

mercaptododecaborate (BSH), Polyethylene glycol (PEG)

Acknowledgements:

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References:

[1] M. Shirakawa, H. Tomida, R. Takeuchi, H. Hori, Patent applications 2018-156145, PCT/JP2019/033062.
[2] M. Shirakawa, et. al., Development of novel boron cluster conjugated PEG derivative for BNCT. Poster presented at: 10th Young Researchers BNCT Meeting; Sep 26-29, 2019, Helsinki, Finland.
[3] M. Shirakawa, et al., *KURRI PROGRESS REPORT 2017*, 69, (2018).

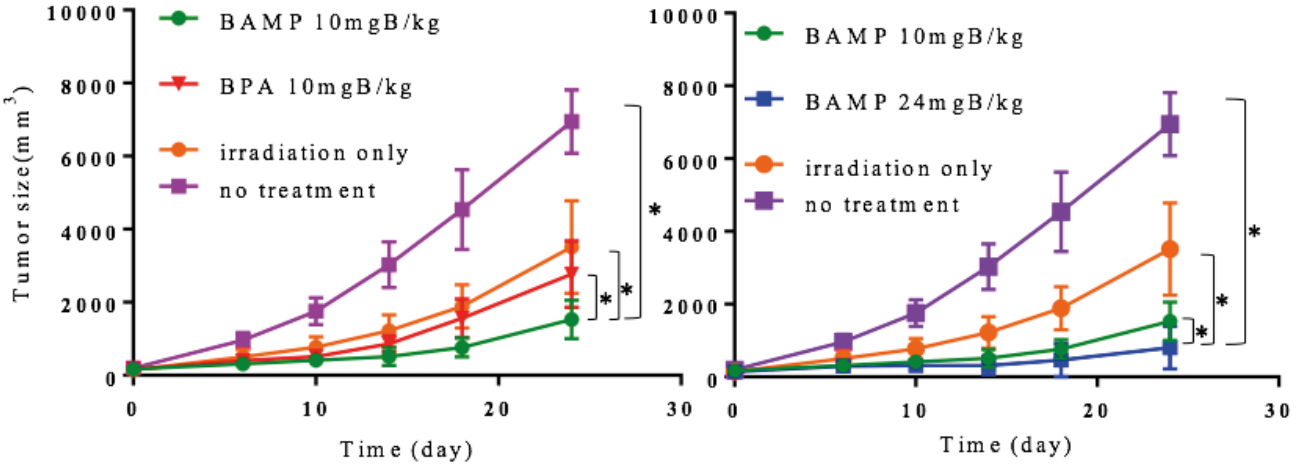

Figure 1. Antitumor effect of the BAMP by thermal neutron irradiation. A significant difference in tumor size on the last measurement day of each group was calculated by independent t-test. The value of the significant difference and the asterisks are as follows. *P<0.05 (BAMP vs. BPA, irradiation only, no treatment).

Tumor growth suppression by gadolinium-neutron capture therapy with intra-tumoral injection of gadolinium-liposome complex(Gd-plex) to pancreatic cancer model *in vivo*

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Purpose : Gadolinium-neutron capture therapy(GdNCT) is a particle beam therapy using gadolinium and thermal neutron. Gadolinium(^{157}Gd) reacts thermal neutron and offers cytotoxic effect by 1mm-range high LET Auger electron, and long-rangegamma rays. Therefore, for effective GdNCT, it is necessary to accumulate Gadolinium atoms into the tumor tissues selectively. In this study, we evaluated gadolinium / hyaluronic acid / protamine-mixed with cationic liposome (^{157}Gd-plex) as neutron capture therapy agent by in vivo experiment on AsPC-1 human pancreatic tumor-bearing mice.

Method : We prepared nanoparticles mixed with 1.5mL of Gadolinium compound "Gadovist" (MW: 604.71), 0.2mL of a solution of 10mg/mL-hyaluronic acid sodium, and 0.1mL of 20mg/mL of protamine incubating at room temperature for 30min. Then, these mixing solutions were poured into Coatsome EL-C. We prepared human pancreatic cancer AsPC-1($5x10^5$) model by transplanting to right lower leg. Twelve hours after intra-tumoral injection of 0.2mL of ^{157}Gd-plex, we performed thermal neutron irradiation at Institute for Integrated Radiation and Nuclear Science, Kyoto University ($1x10^{12}$ n/cm^2).

Result : The ^{157}Gd concentration in the ^{157}Gd-plex was 13700ppm by measured ICP-AES, and the diameter of liposome was 200nm. Thirty percent of tumor growth suppression was achieved in the ^{157}Gd-plex injected NCT group compared with non-irradiated group. The tumor growth suppression of the ^{157}Gd-plex injected group was superior than the only Gdovist injected group by NCT.

Conclusion : We attempted enhancement of retention of gadolinium atoms by mixing ^{157}Gd-plex. The experimental results showed that the tumor growth suppression of ^{157}Gd-plex-injected irradiated group was revealed superiority compared to the group with ^{157}Gd solution injection, or non-treated control group after NCT, and no significant weight loss were observed after treatment suggesting low systemic toxicity of this system. We would like to consider the best irradiation time and dose of administration. The ^{157}Gd-plex will become one of the candidates for ^{157}Gd delivery system on NCT.

	Tumor growth rate			
	Day6	Day10	Day13	
Non-NCT				
^{157}Gd solution	1.79±0.34	3.92±1.33	4.64±1.64	
^{157}Gd-plex mix	1.41±0.17	2.26±0.18	2.62±0.03	
Non-treated	1.62	2.02	3.21	
NCT				
^{157}Gd solution	1.55±0.38	2.29±0.67	2.50±0.42	25% suppress
^{157}Gd-plex mix	1.58±0.71	1.82±0.81	2.14±0.93	31% suppress
Non-treated	1.62±0.06	2.30±0.27	2.64±0.07	

30% suppress

Figure 1. Tumour growth suppression by GdNCT with intra-tumoral injection of 157Gd-plex to AsPC-1 pancreatic cancer model.

Keywords:

Drug Delivery System, Cationic liposome, Hyaluronic acid / Protamine complex, Intra-tumoral injection, Gadolinium Neutron Capture Therapy

References:

[1] Y. Sekine. Progress in Drug Delivery System IX, **2000**; pp23-30.
[2] D. Novriana. J Cancer Res Clin Oncol. **2016**, 142:767-775.
[3] K. Maruyama. Biomaterials **2004**, 25:3267-3273.
[4] S. Harada. Biomed. & Pharmacother. **2015**, 70:196-205.

Biology

Biology

Usefulness of combination with both continuous administration of hypoxic cytotoxin, tirapazamine and mild temperature hyperthermia in boron neutron capture therapy in terms of local tumor response and lung metastatic potential

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Purpose: To evaluate the usefulness of combined treatment with both continuous administration of a hypoxic cytotoxin, tirapazamine (TPZ) and mild temperature hyperthermia (MTH) in boron neutron capture thrrapy (BNCT) in terms of local tumor response and lung metastatic potential, referring to the response of intratumor quiescent (Q) cells.

Methods and Materials: B16-BL6 melanoma tumor-bearing C57BL/6 mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all proliferating (P) cells. The tumors received reactor thermal neutron beam irradiation following the administration of a **10**B-carrier (*L-para*-boronophenylalanine-**10**B (BPA) or sodium mercaptoundecahydrododecaborate-**10**B (BSH)) after single intraperitoneal injection of an acute hypoxia-releasing agent (nicotinamide), mild temperature hyperthermia (MTH, 40 °C for 60 min), 24h continuous subcutaneous infusion of TPZ or combined treatment with both TPZ and MTH. Immediately after irradiation, cells from some tumors were isolated and incubated with a cytokinesis blocker. The responses of the Q and total (= P + Q) tumor cell populations were assessed based on the frequency of micronuclei using immunofluorescence staining for BrdU. In other tumor-bearing mice, 17 days after irradiation, macroscopic lung metastases were enumerated.

Results: BPA-BNCT increased the sensitivity of the total tumor cell population more than BSH-BNCT. However, the sensitivity of Q cells treated with BPA was lower than that of BSH-treated Q cells. With or without a **10**B–carrier, combination with continuously administered TPZ with or without MTH enhanced the sensitivity of the both total and Q cells, especially Q cells. Even without irradiation, nicotinamide treatment decreased the number of lung metastases. With irradiation, BPA-BNCT, especially in combination with combined treatment with both TPZ and MTH as well as nicotinamide treatment, showed the potential to reduce the number more than BSH-BNCT.

Conclusion: BSH-BNCT combined with TPZ with or without MTH improved local tumor control, while BPA-BNCT in combination with both TPZ and MTH as well as nicotinamide is thought to reduce the number of lung metastases. It was elucidated that control of the chronic hypoxia-rich Q cell population in the primary solid tumor has the potential to impact the control of local tumors as a whole and that control of the acute hypoxia-rich total tumor cell population in the primary solid tumor has the potential to impact the control of lung metastases.

Keywords:
Boron neutron capture therapy; **10**B-carrier; quiescent tumor cell; tirapazamine, nicotinamide; mild temperature hyperthermia

Accelerator-based boron neutron capture therapy: *in vivo* experiments.

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The report is about an assessment of a beam at an accelerator neutron source at Budker Institute of Nuclear Physics and its possible application on glioblastoma tumor. An evaluation of the efficacy of boron neutron capture therapy on heterotopic glioblastoma U87 MG in SCID mice using different boron containing drugs was carried out. Accumulation of ^{10}B in tumor and normal tissues was detected using atomic emission spectrometer ICPE-9820 (Shimadzu, Japan). Tumor growth was significantly slower in all irradiated groups from the 7th day after BNCT compared to untreated control group. The differences between experimental groups became significant from the 50th day after BNCT. Liposomal BSH showed better long-term results compared to BPA and non-liposomal BSH.

The study was carried out with the support of the Russian Foundation for Basic Research (grant No. 18-29-01007) using the equipment of the Center for Genetic Resources of Laboratory Animals, Institute of Cytology and Genetics, supported by the Ministry of Education and Science of Russia (Unique identifier of the project is RFMEFI62117X0015). Irradiation at the neutron source was supported by the Russian Science Foundation (grant № 19-72-30005).

Keywords:

boron neutron capture therapy, accelerator based epithermal neutron source; boronophenylalanine, sodium borocaptate, liposomal borocaptate, SCID mice with subcutaneous xenografts of human glioblastoma U87 MG.

Optimization of the blood vessel normalization protocol used for BNCT studies in the hamster cheek pouch oral cancer model

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Introduction: One of the hallmarks of cancer is angiogenesis and neovascularization. Tumour blood vessels are structurally and functionally different from the normal vasculature, as they are immature, malformed, tortuous, dilated, and leaky. These abnormalities contribute to a heterogeneous blood flow, interstitial hypertension, hypoxia, and acidosis. Deficient blood supply and elevated interstitial fluid pressure result in a poor distribution of blood-borne therapeutic agents and, in the case of BNCT, would affect the distribution of boron delivery agents in the tumour. Boron targeting of the largest possible proportion of tumour cells contributes to the success of BNCT. Our group demonstrated, in the hamster cheek pouch oral cancer model, that thalidomide induced aberrant blood vessel normalization and improved boron distribution in tumour and significantly enhanced BPA/BNCT tumour control [1]. Thalidomide is an antiangiogenic agent, with anti-cancer and anti-inflammatory effects, approved for its use in humans. However, thalidomide is highly soluble in dimethilsulfoxide -DMSO- which negatively affects animal welfare [2].

Materials and methods: Tumour bearing hamsters (cancerized with 0.5% dimethylbenzanthracene in mineral oil, 24 applications [3]) were subjected to different protocols adapted from the literature: (A) Thalidomide "classical" protocol (112 mg thalidomide/ml DMSO, [2]) at 48 h and 24 h before euthanasia and necropsy (200 mg thalidomide/kg body weight -bw-, intraperitoneal injection -ip-) (n= 3 animals); (B) topical application of thalidomide in mineral oil (112 mg thalidomide/ml mineral oil), at 24 h (200 mg thalidomide/kg bw) (n= 3); (C) topical application of thalidomide in mineral oil (112 mg thalidomide/ml mineral oil), at 96 h, 72 h, 48 h and 24 h (200 mg thalidomide/kg bw) (n= 5); (D) control group: topical application of mineral oil during four days (n=5); (E) topical and oral application of thalidomide in mineral oil (112 mg thalidomide/ml mineral oil), at 96 h, 72 h, 48 h and 24 h (400 mg thalidomide/kg bw) (n= 3); (F) 100 mg of thalidomide in 250 µl DMSO (1/4 of the volume used in (A)), at 48 h and 24 h (200 mg thalidomide/kg bw, ip) + meloxicam (anti-inflammatory drug, 0.2 mg/kg bw) and lidocaine 2% (for local anaesthesia, 1 mg/kg bw) (n= 10); (G) same as F, but without meloxicam or lidocaine. Body weight, clinical signs and tumour response to the treatment protocols were monitored throughout follow-up. Aberrant blood vessel normalization in the precancerous tissue surrounding tumours was assessed by a double-blind macroscopic study.

Results: Protocol (A) exhibited blood vessel normalization in the precancerous pouch tissue. One of the animals died 24 h after the first application of thalidomide (33%). After each thalidomide injection, the animals exhibited somnolence and clinical signs of pain (stooped posture and walking difficulties). Both animals exhibited internal bleeding, intestinal inflammation and adherences. In the mineral oil protocols (B,C,D,E), none

of the animals died during the experiment or exhibited pain but only protocol (E) exerted a slight blood vessel normalization in precancerous tissue. In protocol (F), only one animal died (10%). In all the animals meloxicam reduced the intestinal inflammation and lidocaine helped to reduce the pain due to thalidomide injection. This protocol induced aberrant blood vessel normalization in precancerous tissue similar to the classical thalidomide protocol (A). Protocol (F) induced 84% overall tumour response (reduction in initial tumour volume) at the end of the protocol.

Conclusion: The thalidomide protocol used for our BNCT studies was optimized by reducing the volume of DMSO, increasing animal welfare significantly and inducing a high tumour response. Ongoing studies seek to evaluate the optimized thalidomide protocol in combination with GB-10 in terms of boron microdistribution in tumour and precancerous tissue. BNCT studies will determine the potential therapeutic benefit of this strategy.

Keywords:
blood vessel normalization; oral cancer; thalidomide; animal welfare

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References:

[1] Molinari AJ, Pozzi EC, Monti Hughes A, et al. Tumor blood vessel "normalization" improves the therapeutic efficacy of boron neutron capture therapy (BNCT) in experimental oral cancer. Radiat Res. 2012;177(1):59–68. doi:10.1667/rr2729.1
[2] Molinari AJ, Aromando RF, Itoiz ME, et al. Blood vessel normalization in the hamster oral cancer model for experimental cancer therapy studies. Anticancer Res. 2012;32(7):2703–2709.
[3] Santa Cruz IS, Garabalino MA, Trivillin VA, et al. Optimization of the classical oral cancerization protocol in hamster to study oral cancer therapy. Oral Dis. 2020;10.1111/odi.13358. doi:10.1111/odi.13358

Analysis of the effects of spatial distribution of boron and oxygen concentration on DNA damage in boron neutron capture therapy using monte carlo simulations

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As an advanced binary targeted therapy technology, boron neutron capture therapy (BNCT) has its unique physical and radiobiological advantage. The physical principle of BNCT is based on the production of low-energy and short-range α and ^{7}Li particles based the ^{10}B (n, α) ^{7}Li nuclear reaction [1,2]. Compared with conventional radiotherapy, the mechanism of radiation damage caused by BNCT has seldom been thoroughly studied for either normal or tumor cells. For the sake of simplification, many previous studies did not fully consider the radiosensitivity of cells and enrichment of boron compounds in determining the BNCT biological effects. In our study, we aim to evaluate the biological effects of BNCT by taking into consideration of both physical interactions and radiobiological characteristics of BNCT. The method of combining Geant4 and MCDS model is proposed to analyze radiation damage induced by BNCT for the first time. The effects of the spatial distribution of boron in cells and oxygen concentration on the DNA damage and RBE of DSB have been investigated.

The DNA damage induced by all charged particles in BNCT was evaluated by combining Geant4 (Geant4 10.05.p01) and Monte Carlo Damage Simulation software (MCDS 3.10A). The kinetic energy spectra of α and ^{7}Li particles in BNCT arriving at the nucleus surface were obtained from Geant4 Monte Carlo simulation. Recoil protons were produced by hydrogen atoms capturing fast neutrons, whose spectrum was calculated by irradiating the cylindrical tissue equivalent material with a BNCT neutron source. The DNA damage caused by all charged particles in BNCT with the energy spectra calculated above was then evaluated using MCDS. Finally, the RBE of DSB induction in BNCT was determined with the ^{137}Cs X-rays as the reference radiation.

When the initial emission positions of α and ^{7}Li particles were different, the proportion of different DNA damage types was also different. The change of oxygen concentration had very little effect on the number of DNA damage induced by α and ^{7}Li particles, but their relative biological effectiveness (RBE) decreased with the increase of oxygen concentration. When the oxygen concentration varied from 0% to 50%, the DSB induced by recoil protons was increased by 49.42%, whereas it was increased by 85.35% by 0.54 MeV protons, that were generated from the capture of the thermal neutrons by nitrogen atoms, and the calculated RBE of 0.54 MeV protons and recoil protons decreased from 5 to 2.

Compared to α and ^{7}Li particles, the effect of oxygen concentration on DNA damage induced by 0.54 MeV protons and recoil protons was more significant in BNCT, and the RBE of all charged particles decreased gradually with the increase of oxygen concentration, this trend was reasonable consistent with the previous experimental data. These findings indicate that the RBE of different particles formed during BNCT might be affected by many

factors, which should be considered in development of new boron compounds, dose calculations and treatment planning.

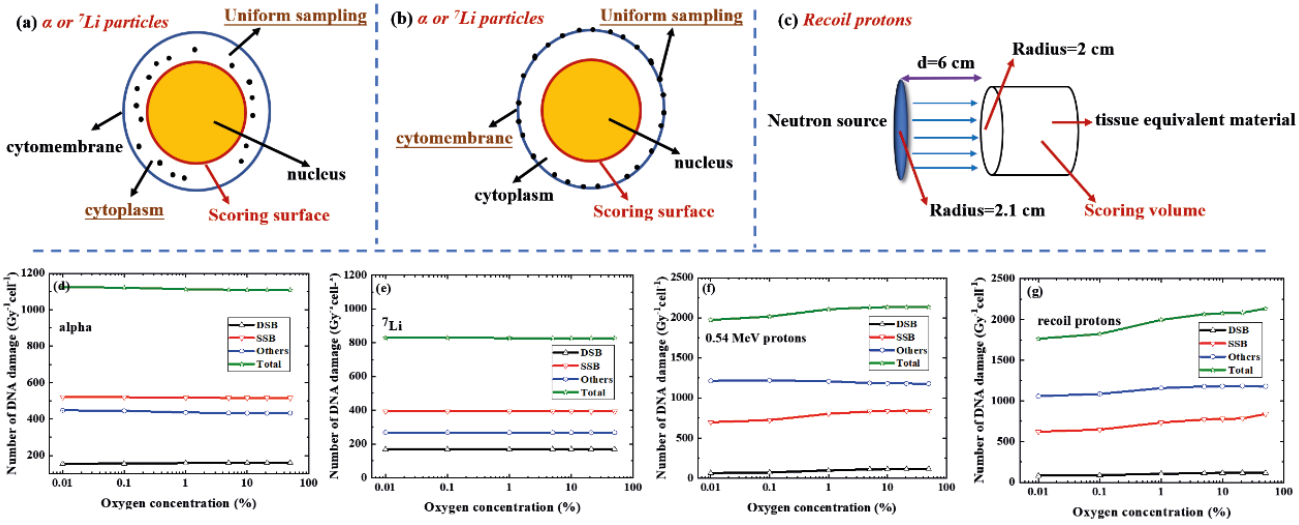

Figure 1. Models configuration in Geant4 Monte Carlo simulations and number of DNA clustered damage under different oxygen concentrations. Process of recording the energy spectrum distribution of α or ^{7}Li particles arriving at the surface of nucleus when they were evenly distributed in the cytoplasm (a) or cytomembrane (b); process of recording energy of recoil protons in equivalent tissue material when it was irradiated by Massachusetts Institute of Technology (MIT) neutron source (c). Number of DNA clustered damage under different oxygen concentrations caused by the radiation of α particles (d), ^{7}Li particles (e), 0.54 MeV protons (f), and recoil protons (g) calculated by MCDS.

Keywords:

Monte carlo simulations; BNCT; boron distribution; MCDS; DNA damage

References:

[1] Moss RL. 2014. Critical review, with an optimistic outlook, on Boron Neutron Capture Therapy (BNCT). Appl Radiat Isot. 88:2–11.

[2] Barth RF, Coderre JA, Vicente MGH, Blue TE. 2005. Boron neutron capture therapy of cancer: current status and future prospects. Clin Cancer Res. 11(11):3987–4002.

[3] Ono K. 2015. Boron Neutron Capture Therapy (BNCT) Breaks New Ground for Cancer Radiotherapy.

Study of the influence on normal liver tissue by boron neutron capture therapy

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Introduction

Boron neutron capture therapy (BNCT) for liver tumor, which has been conducted up to the present, has used the compound effectiveness factor (CBE) determined by using genotoxicity for hepatocytes as an indicator, which has been clarified by Suzuki et al [1]. But there is a problem whether it is appropriate as a real clinical endpoint. Fundamental researches of liver fibrosis that are the late effect of radiation therapy are necessary. It is necessary to do basic research that uses liver fibrosis, which is a late radiation injury to the liver, as an evaluation index. The hedgehog signaling pathway is one of the important processes involved in animal development, and has been implicated in the maintenance and regeneration of adult tissues. The hedgehog signaling pathway is activated in the damaged liver and affects tissue remodeling. It has also been reported that cell proliferation is promoted and epithelial-mesenchymal transition leading to fibrosis is induced [2]. A purpose of this study is to find the early indicator or surrogate marker which cause fibrosis in the normal liver tissue after BNCT.

Materials and Methods

Female C57BL6 mice at 6weeks of age were injected 1,000 mg/kg p-boronophenylalanine (BPA) solution subcutaneously 2 hours before neutron irradiation. The mice were irradiated for 60 minutes at the 1MW output. One week after irradiation, mice were sacrificed and the blood and livers were analyzed. Blood and liver boron concentrations 2 hours and 3 hours after the administration of 1,000 mg/kg BPA were quantified using Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES). In addition, Masson trichrome staining was performed to determine the degree of liver fibrosis six months after neutron irradiation. Hematoxylin Eosin (HE) staining and triglyceride quantification were performed to investigate degree of the steatosis in the mouse normal liver tissue after BNCT. Western blotting was performed to determine the expression level of Sonic Hedgehog protein.

Results

Two hours after the administration of BPA, the liver boron concentration was about 8.1 μg/g, and the blood boron concentration was about 9.2 μg/g. Three hours after BPA administration, the liver boron concentration was about 4.1 μg/g, and the blood boron concentration was about 4.4 μg/g. Masson trichrome staining showed a tendency for increased liver fibrosis in the neutron-irradiated group receiving BPA (BNCT group). The result of HE staining demonstrated that the steatosis of the BNCT group was increased. Triglycerides in mouse normal liver tissue after BNCT tended to be increased compared to control. Furthermore, as a result of Western blotting, the expression of Sonic Hedgehog protein in the BNCT group was higher than in the group only irradiated with neutrons.

Conclusion

It was revealed that the expression of Sonic Hedgehog increased in response to liver injury by BNCT and was involved in liver fibrosis. The results of this study suggest that hepatocellular steatosis may be an early indicator or surrogate marker for evaluating adverse events related to liver fibrosis in BNCT.

Keywords:

BPA, Liver, steatosis, Sonic Hedgehog

References:

[1] Suzuki M et al. The Effect of Boron Neutron Capture Therapy on Liver Tumors and Normal Hepatocytes in Mice. *Jpn. J. Cancer Res.* 2000, 91, 1058-1064.

[2] Jung Y et al. Signals from dying hepatocytes trigger growth of liver progenitors. *Gut* 2010, 59, 655-665

BNCT for veterinary medicine.

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We provided clinical veterinary BNCT studies in cats and dogs with spontaneous malignant tumors on accelerator based epithermal neutron source at Budker Institute of Nuclear Physics in Novosibirsk, Russia and IRT-T research reactor at National Research Tomsk Polytechnic University in Tomsk, Russia.

These animals were selected for this method of therapy due to the impossibility of performing surgical treatment and other methods of therapy. BSH (Katchem, Czech Republic) was used as boron compound at a dose of 100 mg / kg, intravenous infusion lasting 1 hour. Before and after irradiation, blood samples were taken from the animal to study the boron concentration with an ICPE-9820 atomic emission spectrometer (Shimadzu, Japan). A preliminary calculation of the dose in the tumor and skin was carried out using the tomography data by the Monte Carlo method. In all cases, we observed partial tumor response, clinical benefit, and an increase in estimated survival time when recruited with excellent quality of life. Treatment-related toxicity was mild and reversible. These studies contribute to the preparation for clinical trials of BNCT for the treatment malignant tumors in Russia and suggest a potential role for BNCT in veterinary medicine.

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Keywords:
veterinary medicine, bnct, malignant tumors, cats, dogs, accelerator based epithermal neutron source, research reactor, IRT-T

Polymer-stabilized elemental boron nanoparticles for BNCT: cell irradiation experiments.

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The boron compounds currently used in clinical and preclinical BNCT experiments, BSH and BPA, do not meet all the desired criteria for ideal treatment. Their imperfections motivate scientists to search for new solutions that better meet the requirements, one of which is the delivery of sufficient amounts of boron to tumor cells to reach a ^{10}B concentration of ≥ 20-30 μg/g in tumor tissue. Without addressing tumor-targeting issues, loading tumor tissue with a sufficient amount of boron can be solved using nanoparticles that contain large numbers of boron atoms per particle, compared to 1 or 12 boron atoms per molecule of BPA or BSH, respectively. Thus, a 3 nm nanoparticle contains ~ 120 thousand ^{10}B atoms and a 50 nm nanoparticle can deliver about 2 million ^{10}B atoms.

Here. we report on irradiation experiments using elemental boron nanoparticles (eBNPs) synthesized by a new method of cascade ultrasonic dispersion/destruction of elemental boron micron particles (10-20 microns) in an aqueous medium and stabilized with hydroxyethyl cellulose. BPA was used as a control. Transmission electron microscopy was used for particle visualization. Cytotoxicity analysis by MTS assay showed no obvious toxicity up to high nanoparticle concentrations in T98 human glioma cells. For irradiation experiments, the cells were incubated with nanoparticles or BPA in different concentrations for 24 hours, washed with PBS, trypsinized, centrifuged, collected, and then placed in 1ml plastic vials in the medium they were incubated with to avoid BPA leakage from the cells. The plastic vials with cells were placed in a plexiglass phantom to imitate the human head and provide the maximum thermal neutron fluence at the level of the vials. Neutron irradiation was performed at an accelerator-based neutron source with a subsequent colony-forming assay to evaluate cell survival. Cell-survival curves were fit to the linear-quadratic (LQ) model and radiobiological parameters were calculated.

The synthesized nanoparticles demonstrated tumor cell-killing effects significantly superior to those demonstrated by BPA using the same boron concentrations in the incubation medium. These preliminary results show the superiority of nanoparticle-based boron delivery for BNCT and warrant further tumor targeting-oriented modifications of the synthesized particle and subsequent in vivo experiments.

The study is ongoing and a more detailed description will be provided at the conference.

Keywords:
elemental boron, nanoparticles, polymer stabilization, neutron irradiation, accelerator-based neutron source.

O81

Local therapeutic efficacy, abscopal effect and cytotoxicity of BNCT mediated by BPA+GB-10 using Oligo-Fucoidan and Glutamine as adjuncts in an ectopic colon cancer model

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The aim of the present study was to evaluate the overall effect of BNCT mediated by borophenylalanine (BPA)+ sodium decahydrodecaborate (GB-10) using Oligo-Fucoidan and Glutamine as adjuncts in an ectopic colon cancer model in terms of local therapeutic efficacy, abscopal effect (out-of-field effect) and cytotoxicity. BDIX rats were inoculated subcutaneously with syngeneic colon cancer cells in the right hind flank. Four weeks post-inoculation the tumor bearing rats were treated at RA-3 Nuclear Reactor, Buenos Aires, Argentina, as follows:

a) (BPA+GB-10)-BNCT: (BPA) 31 mg ^{10}B /kg + (GB-10) 34 mg ^{10}B/kg, i.v.

b) (BPA+GB-10)-BNCT + Oligo-Fucoidan: (a) + Oligo-Fucoidan (200 mg/ml) once a week for 7 weeks, joint oral-topical administration.

c) (BPA+GB-10)-BNCT + Glutamine: (a) + Glutamine (40 mg/ml) once a week for 7 weeks, with wet compresses.

d) Sham: same manipulation, untreated.

Two weeks post-BNCT, colon cancer cells were inoculated in the contralateral left hind flank to assess abscopal effect. Tumor volume was measured in both legs weekly. Seven weeks post-BNCT the animals were euthanized for evaluation. A cytotoxicity test was carried out with splenocytes and colon tumor cells.

The post/pre-BNCT ratio of tumor volume at 7 weeks post-treatment as an indicator of local therapeutic efficacy was significantly lower for all the groups treated with BNCT vs SHAM ($p < 0.05$), i.e. SHAM: 9.1 ± 1.9 n=5; BNCT: 0.5±0.5 n=7; BNCT+Oligo-Fucoidan: 0.4±0.2 n=5; BNCT+Glutamine: 1.0±1.9 n=5. The incidence of animals with a mean tumor volume below an arbitrary value of 65 mm^3 in the left (non-irradiated) leg was taken as an indicator of abscopal effect. The incidence was 0% for the Sham group, 67% for BNCT, 50% for BNCT+Oligo-Fucoidan and 25% for BNCT+Glutamine. Albeit the small sample size (3-4 animals per group) that precludes an adequate statistical analysis, these values suggest an abscopal effect of BNCT and BNCT+Oligo-Fucoidan/Glutamine that warrants further studies. The mean cytotoxicity level of the Sham group was below the value for the normal (no tumor) animals. Our working hypothesis was that treated animals would show cytotoxicity levels above normal. The incidence of animals with cytotoxicity levels above normal was 20% for Sham, 57% for BNCT, 60% for BNCT+Oligo-Fucoidan and 80% for

BNCT+Glutamine. Although these differences did not reach statistical significance, conceivably due to the small sample size, they express a trend that warrants further studies. The incidence of severe dermatitis at two weeks was 100% for (BPA+GB-10)-BNCT alone, while Oligo-Fucoidan reduced incidence to 80 % and Glutamine reduced incidence to 40%, the latter reduction being statistically significant vs. (BPA+GB-10)-BNCT alone ($p<0.05$).

The present study suggests that the local therapeutic efficacy of (BPA+GB-10)-BNCT in the rat ectopic colon cancer model is associated to an abscopal effect and an increase in cytotoxicity values above those in normal animals. Oligo-Fucoidan and Glutamine may be useful adjuncts to enhance therapeutic efficacy and/or reduce toxicity either directly or indirectly by reducing the dose necessary to induce the same therapeutic effect.

Keywords:
BNCT, Abscopal Effect, Oligo.Fucoidan, Glutamine, Citotoxicity, BPA, GB-10, BPA+GB-10, Dermatitis.

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O84

Basic experiments to expand the therapeutic application of boron neutron capture therapy (BNCT) for primary central nervous system lymphoma (PCNSL)

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Background: Boron neutron capture therapy (BNCT) is a nuclear reaction-based tumor cell-selective particle irradiation that occurs when nonradioactive boron-10 is irradiated with low-energy neutrons to produce high-energy α particles (^{10}B [n, α] ^{7}Li). BNCT has been clinically applied to invasive cancers such as high-grade glioma, meningioma, melanoma, and head and neck cancer. Primary central nervous system lymphoma (PCNSL) accounts for 5% of all primary brain tumors and like high-grade glioma, is classified as a WHO Grade IV. In order to expand the indications of BNCT and to confirm its efficacy and safety for PCNSL, we conducted a basic experiment of BNCT.

Methods: Cellular boron concentration in Raji human lymphoma cells was measured after 24 hours of exposure to boronophenylalanine (BPA). Raji lymphoma cell suspension has been inoculated into the brain of nude mouse to evaluate the bio distribution of boron after systemic administration (i.p.) of BPA in experimental mouse PCNSL models. In neutron irradiation studies, we evaluated the therapeutic effect of BNCT on mouse PCNSL models in terms of survival by dividing the mouse into untreated, BPA i.p. only, neutron irradiated only, BPA + irradiated groups.

Results: In vitro, Raji lymphoma cells showed a high capacity for boron uptake as glioma cells after exposure to BPA. In the biodistribution study using the Raji human lymphoma cell-bearing mouse brain tumor model, the boron concentration of the tumor was higher than that of the surrounding normal brain, but it was not sufficient. In the neutron irradiation experiment, there were statistically significant differences between the BNCT using BPA group and untreated or irradiate without boron group.

Discussion: The treatment of PCNSL is based on chemotherapy with high-dose methotrexate (HD-MTX) and whole brain irradiation. However, while the initial response rate is relatively good, up to 86%, the recurrence rate is high and there is also the problem of neurotoxicity such as cognitive dysfunction as long-term side effects of WBRT due to combination with these chemotherapy is not well tolerated and suited. Because of the problems of neurotoxicity, there is no useful treatment for PCNSL at relapse. There is a wide range of intracranial diseases that can be “treated” with BNCT, not limited to gliomas. In our experience, FBPA positron emission tomography (PET) has shown high enough accumulation of FBPA in primary malignant lymphoma of the central nervous system. Fortunately, lymphomas are known to be highly radiosensitive and do not require very high doses. Rather, radiotherapy modalities that can be safely delivered multiple times are suitable. That is why BNCT is considered to be an effective treatment for recurrent PCNSL. The present experiments showed that lymphoma cells have good boron uptake capacity and bio distribution, and that BNCT was shown to be effective for experimental

mouse PCNSL models in neutron irradiation study. As PCNSL is a whole brain disease, basic research will be carried out on this disease, including developing specific neutron irradiation methods in the future.

Keywords:
Boron neutron capture therapy (BNCT), Primary central nervous system lymphoma (PCNSL)

O91

Effectiveness of 18kDa translocator protein (TSPO) targeting novel boron compound for boron neutron capture therapy in rat experimental brain tumor model

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Background

Boron neutron capture therapy (BNCT) is a treatment based on the nuclear reaction known as boron neutron capture. The reaction produces high linear energy transfer particles and destroy boron-10 (^{10}B) acquiring tumor cells selectively. Previously, our research group has shown the effectiveness of BNCT in several clinical trials for malignant gliomas. Boronophenylalanine (BPA) was mainly used for these trials, however malignant gliomas which have the characteristic of invasion to the surrounding normal brain tissue were unable to cure completely and further improvement of therapeutic efficacy of BNCT is expected. Recently, tracers targeting 18kDa translocator protein (TSPO) were found to be highly accumulated in malignant gliomas by positron emission tomography (PET) study. Furthermore, it has been reported that the PET scan targeting TSPO has the potential to predict recurrence of malignant gliomas before recurrence as enhanced lesion with standard contrasted MRI. We hypothesized that TSPO might be a novel target for BNCT of malignant gliomas.

Materials and Methods [1, 2]

At first, TSPO expressions were evaluated both in vitro and vivo using Western blot analysis and real-time polymerase chain reaction for the rat glioma cell-lines. In vitro, the cellular uptake of ^{10}B in F98 glioma cells and several malignant tumor cell-lines were measured. The biological effectiveness factors specific for ^{10}B compounds targeting TSPO (named DPB15) with neutron capture reaction were calculated for F98 rat glioma cells. In vivo, biodistribution for the F98 rat glioma models were evaluated by administration of ^{10}B compounds (BPA (i.v.; intravenous administration) or DPB15 (CED; convection-enhanced delivery)). Neutron irradiation experiments for the F98 glioma-bearing rat brain tumor models were performed and evaluated by Kaplan-Meier survival curves and median survival times were compared between each group. In neutron irradiation experiments, the F98 rat glioma models were divided to six groups; untreated controls, neutron irradiation only controls, DPB15 only controls, BNCT with BPA, BNCT with DPB15, and BNCT with combination of BPA and DPB15.

Results

TSPO expression had been confirmed in F98 and C6 rat glioma cells by Western blot. And in the F98 rat glioma models, TSPO showed 16 times higher expression in the tumor than contralateral normal brain tissue. In vitro, the calculated biological effectiveness factors of DPB15 were the highest compare with BPA or BSH. In vivo biodistribution study, systemically administered DPB15 by i.v. was enough safe but have not obtained the tumor boron

concentrations. DPB15 administered by CED group showed > 2 times higher tumor boron concentrations than i.v. BPA (45.0 ± 20.6 vs 20.6 ± 2.6μg/g, respectively). The median survival time was significantly prolonged in the BNCT with DPB15 group compared to the untreated controls group (21.0 vs 28.0 days, respectively, log-rank test; p = 0.0008). The combination group (BNCT with combination of BPA and DPB15) had significant longer survival times than single BPA group (33.5 vs 31.5 days, respectively, log-rank test; p = 0.0187).

Conclusion

Several techniques have already been developed to visualize malignant gliomas in PET using tracers targeting TSPO. Therefore, as with ^{18}FBPA-PET, it is possible to select patients suitable for BNCT with this agent. Since TSPO is highly expressed in malignant gliomas, the uptake of ^{10}B compounds targeting TSPO is increased, making it a valuable target for which BNCT should be fully utilized. The combination CED administration of compounds targeting TSPO and the intravenous administration of BPA may destroy the cells that had been not destroyed BNCT with BPA and improve the effectiveness for BNCT of malignant gliomas.

Keywords:

Boron neutron capture therapy (BNCT), 18kDa translocator protein (TSPO), malignant glioma, FBPA-PET, convection-enhanced delivery (CED)

References:

[1] Fukuo Y, Hattori Y, Kawabata S, Kashiwagi H, Tanaka H, Suzuki M, Miyatake SI, Kirihata M, Wanibuchi M, et al. Biology (Basel). 2020; 9(12): 437.

[2] Takeuchi K, Hattori Y, Kawabata S, Futamura G, Wanibuchi M, Tanaka H, Miyatake SI, Kirihata M, et al. Cells. 2020; 9(6): 1551.

O104

Biological experiments by the dual phantom technique for the assessment of fast-neutron effect on brain tumor cells in BNCT irradiation field

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INTRODUCTION: Development in several types of accelerator-based irradiation systems for boron neutron capture therapy (BNCT) is underway. Many of these systems are nearing or have started clinical trials. Before the start of treatment with BNCT, the relative biological effectiveness (RBE) for the fast neutrons (over 10 keV) incident to the irradiation field must be estimated. Measurements of RBE are typically performed by biological experiments with a phantom. Although the dose deposition due to secondary gamma rays is dominant, the relative contributions of thermal neutrons and fast neutrons are virtually equivalent under typical irradiation conditions in a water and/or acrylic phantom. Uniform contributions to the dose deposited from thermal and fast neutrons are based in part on relatively inaccurate dose information for fast neutrons.

The aim of this study is the establishment of accurate beam-quality estimation method mainly for fast neutrons by using two phantoms made of different materials, in which the dose components can be separated according to differences in the interaction cross-sections. The fundamental study of a "dual phantom technique" for measuring the fast neutron component of dose is reported [1]. Verification experiments for the dual phantom technique were performed using Heavy Water Neutron Irradiation Facility installed in Kyoto University Reactor (KUR-HWNIF). Biological experiments were performed using the solid phantoms, which were made based on the simulation results.

MATERIALS AND METHODS: One of the dual solid phantoms was made of polyethylene with natural lithium fluoride for 30 weight percent (LiF-polyethylene phantom), and the other phantom was made of polyethylene with 95%-enriched lithium-6 fluoride for 30 weight percent (^{6}LiF-polyethylene phantom).

Human glioblastoma cells, U87 *ΔEGFR* in vials were placed at the surface, 2-cm depth, 5-cm depth and 8-cm depth in the phantoms on the center axis of the beam line, then irradiated. Cell viability assay was performed for the irradiated cells. The cells were divided in two groups regarding drug treatment with or without boronophenylalanine (BPA) at 25 ppm for bolon-10.

The neutron flux and gamma-ray dose rate were measured using activation foils and thermo-luminescent dosimeter, respectively. The depth dose distributions for the thermal neutron, fast neutron and gamma-ray components were determined based on the simulation calculation results normalized referring to the measured values.

RESULTS: In the LiF-polyethylene phantom, the difference for the cell survival was detected between BPA (+) group and BPA (-) group. Due to the neutrons thermalized in this phantom, the cell survival for BPA (+) group was lower than that for BPA (-) group. On the other hand, in the ^{6}LiF-polyethylene phantom, the cell-survival distributions for BPA (+) group and BPA (-) group were almost the same, because most of the thermalized neutrons were absorbed by ^{6}LiF.

CONCLUSION: The assay results will be more analyzed in association with the data of the depth dose distribution for the thermal neutrons, fast neutrons and gamma-rays.

Keywords:
dual phantom technique, enriched lithium-6, biological experiment, fast-neutron effect, cell viability assay

Acknowledgment:
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References:
[1] Y. Sakurai et al., Med. Phys. 42 (2015) 6651-6657.

O105

The three dimentional oral model for pre-clinical investigations in BNCT

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Background:

Boron neutron capture therapy (BNCT) is expected as a new modality for the minimally invasive cancer treatment. The development of boron agents and neutron source for BNCT requires the evaluation system bridging the gap between in vivo and in vitro research. From the viewpoint of the animal welfare and the 3Rs: Replacement, Reduction and Refinement, the humane alternative research methods that do not use animals, are essential for BNCT. On the other hand, three-dimensional (3D) models have been widely used in cancer research due to their ability to mimic multiple features of the tumor microenvironment [1]. This study aimed to investigate the validity of the 3D cancer model for pre-clinical test in BNCT.

Materials and Methods:

For the experiment of boron neutron capture reaction (BNCR) in 2D, 3D, and animal model, human oral squamous cell carcinoma (SAS, JCRB) as cancer cells, and Boronophenylalanine (BPA, Borofaran, Stella pharma) as Boron-10 (boron group) or Saline as control, were used. For the development of oral cancer 3D model, the oral mucosal fibroblast cells (Niigata University) and SAS were embedded and cultured on collagen (Niita-gelatin, Japan) [2]. For mouse tumor-bearing model, SAS were subcutaneously injected into the left hind legs of 6-week-old female Balb/c nude mice (Clea Japan Inc., Japan). All models were treated by BPA or saline and irradiated with neutron. The effect of BNCR in 2D model using colony formation assay, in 3D model using histological examinations, and in animal model using tumor size were compared.

Results:

The number of colonies in boron group is significantly lower compare with control in 2D model. The number of SAS cells in boron group is also significantly lower compared with control in 3 D model. In vitro test indicated that the SAS cell's ability of boron group is lower compared with control in both 2 D and 3 D model. The histological examination of the oral cancer 3 D model revealed that the epithelial thickness of SAS cell layers on the top of the fibroblasts embedded collagen gel was thinner compared with control, however the thickness of fibroblast embedded collagen gel did not differ between the two. The histological images between 3D model and animal model, were similar and the cancer cells were rare in boron group compared with control. In vivo test showed that the tumor growth rate of Boron group is lower compare with control.

Conclusion:

These results indicate the 3D oral cancer model would be useful to evaluate the BNCR and also to bridge the gap between in vitro and in vivo research. Therefore, the 3D model could be an alternative tool to animal test for BNCR. Using the 3D model of rare diseases, it is possible to evaluate for BNCT in near future.

Keywords:
Three-dimensional model, evaluation system, rare diseases

References:

[1] F D Modugno et al., Journal of Experimental & Clini-cal Cancer Research 38:117 (2019)
[2 K.Izumi et al. cells Tissues Organs 176:134-152 (2004)

O111

Functionalized nanovectors for future radiotherapy

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Modern cancer therapies, mainly ionizing radiation and certain classes of chemotherapies, target DNA. Nevertheless, cancer cells can survive by over-activating a wide range of DNA repair pathways to remove the induced damage. In this context, DNA repair is considered a vital target to improve cancer therapy by reducing the resistance to many DNA damaging agents currently in use as standard treatments. Therefore, the development of specific ways to inhibit DNA repair in cancer cells is often referred to as the next major step to improve cancer therapy. It has been unequivocally shown that DNA double strand-breaks (DSBs) are the most lethal lesions caused by ionizing radiation and reactive oxygen species by radiotherapy, and the repair pathways for DSBs have been studied in great molecular details. Nevertheless, this understanding of DNA damage responses at the molecular level has yet to be translated to knowledge-based manipulation of the biological responses of cancer cells to therapeutic radiation. Recent advances in the nanotechnology field have led to new applications of nanoscale devices in the diagnosis and treatment of diseases. Nanoparticles are structures in the nanometre scale range. These structures often gain unique properties due to the fact that certain physical and chemical properties of many materials are amplified or completely changed as their size is scaled down to small clusters of atoms. Precious metal nanoparticles are attractive nanovectors because of their inherent properties as possible therapeutic agents, as they can enhance the effects of ionizing radiation via production of photoelectrons and Auger electrons. Moreover, versatile chemical approaches have been developed to functionalize gold and platinum nanoparticles with target molecules that introduce new properties. We have developed a universal designer peptide targeting system for the autonomous translocation of the nanoparticles to the nucleus of targeted cells. This system is capable of inhibiting DNA damage responses, increasing dramatically the efficacy of experimental radiotherapy, and will be discussed in the context of targeted boron delivery for BNCT.

BNCT/GB-10 and BNCT/GB-10+Electroporation for oral cancer: translational studies of therapeutic efficacy at the RA-1 facility

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Introduction: In the treatment of Head and Neck (H&N) tumors using Boron Neutron Capture Therapy (BNCT) it is relevant to evaluate strategies with different borated agents approved for use in humans. We previously demonstrated the feasibility of treating Squamous Cell Carcinoma (SCC) tumors in the oral cancer model in the hamster cheek pouch with BNCT/GB-10, BNCT/BPA and BNCT/BPA+GB-10 in Reactors RA-6 and RA-3 and with BNCT/GB-10 + Electroporation (EP) at RA-3, with encouraging results (e.g. Trivillin et al, 2006 [1]). We showed that EP would improve boron targeting in tumor, improving therapeutic efficacy without enhancing toxicity. The Reactor RA-1 is of particular interest because it has a neutron spectrum that includes a fast neutron component that might contribute to the treatment of SCC. Our previous studies in the facility of the RA-1 Nuclear Reactor consisted in BPA/BNCT experiments in non-cancerized Syrian hamsters and preliminary studies of BPA/BNCT or GB-10/BNCT in cancerized Syrian hamsters, yielding promising results for BNCT efficacy in the RA-1.

Aim: To perform experiments to assess the therapeutic efficacy and radiotoxicity of BNCT *in vivo* in an oral cancer model in the hamster cheek pouch using BNCT/GB-10 and the combination of BNCT/GB-10 + Electroporation (EP) at the thermal facility of RA-1.

Materials and methods: Tumors were induced in the right cheek pouch of Syrian hamsters by topical application of the carcinogen dimethyl-1,2-benzanthracene (DMBA) 0.5% in mineral oil twice a week for 12 weeks. Once the exophytic tumors developed, i.e. SCC, the animals were used for BNCT studies: Group 1) BNCT/GB-10 (50 mg ^{10}B/kg, iv) (n=32 tumors), Group 2) BNCT/GB-10 (50 mg ^{10}B/kg, iv) +EP (10 min. post-administration of GB-10) (n=28 tumors), Group 3) Beam only (n=35 tumors) and EP only (n=38 tumors). Electroporation was performed on each tumor employing the standard EP pulse parameters (8 pulses of 1000 v/cm, 100 µs and 1Hz). Prior to each *in vivo* BNCT study, the volume of each tumor was determined. Tumor volume range was arbitrarily delimited to small tumors (1 mm^3 ≥volume >10 mm^3) and medium/large tumors (volume ≥10 mm^3). Irradiations were carried out 3 hours post-administration of GB-10 in the RA-1 facility with 10 minutes exposures and using a ^{6}Li carbonate shielding. Tumor response and mucositis in precancerous tissue surrounding tumors were evaluated 7, 10, 14, 21 and 28 days post-irradiation. All experiments were approved by CICUAL-CNEA.

Results: 28 days post-irradiation, overall tumor response (complete remission + partial remission) was 53% for BNCT/GB-10 and 75% for BNCT/GB-10+EP. Overall tumor response for EP Only and Beam Only controls was 34 % and 54%, respectively. These differences, however, did not reach statistical significance, conceivably due to the spread in values. Small tumors´ overall tumor response was statistically higher in BNCT/GB-10+EP (90%) vs BNCT/GB-10 (43%), EP Only (18%) and Beam Only (48%). Medium and large tumors exhibited a complete tumor remission of 11% for BNCT/GB-10, 20% for BNCT/GB-10+EP, 0% for Beam only and 0% for EP only. However, while these differences reveal a trend, they did not reach statistical significance. No severe radiotoxicity (mucositis) was observed in the BNCT/GB-10 or BNCT/GB-10+EP protocols at any follow-up time.

Conclusion: These data suggest that BNCT/GB-10+EP carried out at the RA-1 facility might be therapeutically useful for the treatment of head and neck tumors without associated radiotoxicity.

Keywords:
BNCT, Electroporation, GB-10, Head and Neck, Animal Models

Acknowledgments:
The authors wish to acknowledge the expert advice and generous support of the RA-1 Reactor team.

References:

[1] Trivillin VA, Heber EM, Nigg DW, Itoiz ME, Calzetta O, Blaumann H, Longhino J, Schwint AE.Therapeutic success of boron neutron capture therapy (BNCT) mediated by a chemically nonselective boron agent in an experimental model of oral cancer: a new paradigm in BNCT radiobiology. Radiat Res. 2006; 166(2):387-96.

O132

Comparative analysis of the DNA damage response induced by BNCT in human cell lines of different cancers

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Introduction: The Boron Neutron Capture Therapy (BNCT) is a two-steps procedure to treat different cancers. As first step a boron compound with very high propensity to capture neutrons is administrated to the patient. In the second step takes place the irradiation of the tumor area with thermal neutrons. The neutrons cause nuclear fission of the ^{10}B atom resulting in the emission of ^{4}He and ^{7}Li nuclei and gamma radiation causing direct and indirect damage to the DNA. Due to the need to continue researching the molecular pathways involved in the response to DNA damage after BNCT, a study was carried out that hypothesized the existence of an interaction between TGF beta pathway and the ATM-initiated DNA repair pathway. The TGF-beta pathway has as its main effectors the SMAD proteins, which, depending on their type, play a tumor promoter or suppressor role (1). The antitumor role of SMAD2 is documented by forming a complex with SMAD4 to promote apoptosis and prevent tumor development (2). As well as the pro-tumor role of SMAD7 is described by two mechanisms, promoting genomic instability and inhibiting the TGF-beta pathway by acting as a regulator by negative feedback (3).

Materials and Methods: Three human cell lines of colon adenocarcinoma (HT29), undifferentiated thyroid cancer (8505c) and melanoma (M8), were seeded in bottles of 25 cm2 and each one was separated in three groups: 1) BNCT (using 0.925 mM of boronophenylalanine plus neutrons), NCT (neutrons alone) and Control. The irradiation was carried out in RA-3 reactor (Neutron flux of 1.10 10 n / cm2 sec) and the total physical absorbed dose was 3 Gy. After 2 h of incubation at 37 ° C, the total RNA was extracted with Trizol and RT-qPCR was performed for each gene: TGF beta1, SMAD2 SMAD7, ATM and ATR.

Results: In the HT29 cell line the comparison between the BNCT and Control groups showed a significant decrease in the expression of ATM ($p < 0.001$) and SMAD2 ($p < 0.05$) and an increase in the expression of ATR and SMAD 7 ($p < 0.01$). This increase in SMAD7 would be indicator of the activation of the classic repair pathway, which can be contextualized with the decrease in ATM expression and increase in ATR expression. The 8505c cell line showed for the BNCT group a large increase in the expression of SMAD7 while the expression of the rest of the genes decreased significantly; apparently the therapy prevented the activation of the repair pathway even in the stage of the activation of the TGF-beta pathway with which it interacts. Finally, for the M8 melanoma cell line, the BNCT group did not show an increase in the expression of any member of the TGF-beta / SMAD pathway although the ATM gene showed an important increase indicating a repair of the damage.

Conclusions: The existence of an interaction between the TGF-beta pathway and the repair pathway was demonstrated for the first time on BNCT therapy occurring through a dynamic mechanism associated with double strand DNA damage and the key roles of SMAD2, SMAD7, ATM and ATR. The human cancer cell lines have different radiosensitivity to the therapy. The knowledge of the response mechanisms to BNCT will allow improve the treatment.

Keywords:
DNA repair- TGF-beta pathway-cancer-BNCT

References:

(1) Yang J., et al (2009). Cancer research, 69(6), 2185–2190. https://doi.org/10.1158/0008-5472.CAN-08-3961
(2) Zhao M., et al (2018). International journal of biological sciences, 14(2), 111–123. https://doi.org/10.7150/ijbs.23230
(3) Park, S. et al (2015). Cellular and molecular life sciences: CMLS, 72(3), 583–596. https://doi.org/10.1007/s00018-014-1687-z

Isolating the biological effect of nitrogen capture by the irradiation of in-vitro samples at ILL

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The set up prepared at the cold neutron beam at ILL reactor in Grenoble (France) has proven to be very useful for the study of low-energy neutron biological effect and the study of boron compounds. Thanks to the very clean cold neutron beam (few meV) with a high flux (10^{12}neutrons/cm2) with no gamma contamination, joined with the system adapted for cell irradiation, it opened the opportunity to have a low-energy neutron beam with low gamma dose and barely any epithermal dose [1]. This beam, combined with the installation of a biological lab in the same area than the irradiation line, make possible a large quantity of experiments, necessary for a correct extraction of the biological effect after in-vitro irradiation.

Apart from several thermal RBE studies and CBE studies [2,3], this beam allowed for the first time the isolation of the effect of the capture of neutrons in nitrogen 14. Following the technique of isotope labelling, cells were grown in two different conditions, having those ones grown in a special media with the 14N replaced by 15N (insensitive to neutrons). The particular characteristics of the beam allowed seeing a difference, after irradiation, in the effect of those samples with less 14N (labelled samples). Since the epithermal dose is negligible and by the isolation of this effect due to nitrogen capture (i.e. thermal dose), what remains is the one corresponding to the gamma dose. Therefore, the effect due to only de gammas coming from the beam can be also studied from the same experiment and without having to require any previous gamma irradiations.

For these experiments, the 14N accumulation was measured using neutron autoradiography, observing the tracks of the protons and carbon ions. Different irradiations performed along four years (with cells in conditions of labelled and non-labelled), brought a high collection of data necessary to get precise values of the parameters that define the survival after the irradiation and, consequently, the effect that corresponds only to 14N(n,p)14C and only to the gamma dose, independently. The knowledge of these effects will favor the study of the thermal RBE separately from the epithermal one, will allow a better insight of the gamma dose effect in neutron beams and will provide essential data for dosimetry estimations.

Keywords:
radiobiology, RBE,CBE, neutron irradiation, nitrogen capture

References:

[1] Pedrosa-Rivera M., Ruiz-Magaña M. J., Porras I., Praena J. *et al*. (2020). Neutron radiobiology studies with a pure cold neutron beam. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, *462*, 24-31.
[2] Pedrosa-Rivera M., Praena J., Porras I., Sabariego M. *et al*. (2020). Thermal Neutron Relative Biological Effectiveness Factors for Boron Neutron Capture Therapy from In Vitro Irradiations. *Cells*, *9*(10), 2144.
[3] Pedrosa-Rivera M., Ruiz-Magaña M. J., Álvarez P., Porras I., *et al.* (2020). Radiobiology data of melanoma cells after low-energy neutron irradiation and boron compound administration. *Applied Radiation and Isotopes*, *163*, 109205.

Biology

Poster

In vitro BNCT mediated boronophenylalanine evaluation on melanoma and glioma cells.

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To identify the dependence of the efficiency of boron neutron capture therapy on glioma U251 and melanoma SK-Mel28 cell lines neutron irradiation in presence of ^{10}B at the accelerator based epithermal neutron source at Budker Institute of Nuclear Physics was conducted. Cells were incubated with different concentrations of ^{10}B labeled boronophenylalanine to the growth medium for 24 hours. The samples were placed in polymethyl methacrylate phantom on a depth of 36 mm under the neutron-generating target with following irradiation of the cells by neutron flux. Colony forming assay was performed to evaluate clonogenic capabilities of irradiated glioma and melanoma cells. I t showed that ^{10}B increased by irradiation with neutron beam, leads to decrease in cell survival. It showed that the cells surviving decreased with increasing of ^{10}B after irradiation with neutron beam. Concentrations of ^{10}B in U251 and SK-Mel28 cells were detected with atomic emission spectrometer ICPE-9820 (Shimadzu, Japan) that of confirm the dependence of boron accumulation and cell death. The report presents and discusses the results of this investigation.

The study was carried out with the support of the Russian Foundation for Basic Research (grant No. 18-29-01007) using the equipment of the Center for Genetic Resources of Laboratory Animals, Institute of Cytology and Genetics, supported by the Ministry of Education and Science of Russia (Unique identifier of the project is RFMEFI62117X0015). Irradiation at the neutron source was supported by the Russian Science Foundation (grant № 19-72-30005

Keywords:
boron neutron capture therapy, accelerator based epithermal neutron source; boronophenylalanine; glioma and melanoma cell lines.

P28

Cobaltabisdicarbollide [COSAN]-as a boron carrier for BNCT: biodistribution studies in the hamster cheek pouch oral cancer model

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The development of new, more selective, nontoxic, and effective boron delivery agents that can preferentially deliver a high concentration of boron to the tumor tissue with high tumor-to-blood and tumor-to-normal tissue boron ratios is probably the single greatest need for the advancement of BNCT. Within this context, the sodium salt of cobaltabisdicarbollide (Na[*o*-COSAN]) was developed, synthesized and tested *in vitro* and *in vivo* by Fuentes et al. (2018). Biodistribution studies in normal mice showed that Na[*o*-COSAN] exhibited low toxicity and was distributed into many organs, accumulating mainly in the reticuloendothelial system, including liver and spleen. After 1 h, plasma protein interaction leads to the formation of aggregates that accumulate mostly in lung. Our group previously proposed and validated the use of the hamster cheek pouch model of oral cancer to study the radiobiology of BNCT to improve its therapeutic efficacy, in particular for head and neck cancer. The aim of the present study was to perform, for the first time, boron biodistribution studies in a tumor animal model, i.e. in the hamster cheek pouch oral cancer model, with Na[*o*-COSAN] as the boron carrier. The ultimate goal is to contribute to the optimization of BNCT for the treatment of head and neck cancer by improving boron targeting. The hamster oral cancer model allows us to study tumor tissue, the dose-limiting precancerous tissue surrounding tumors and various clinically relevant normal tissues. The hamsters were submitted to a cancerization protocol by topical application of the carcinogen dimethylbenzanthracene in the right cheek pouch and used for biodistribution studies once the exophytic tumors (Squamous Cell Carcinoma) had developed approximately 12 weeks after the initiation of cancerization. Na[*o*-COSAN] was administered as a slow bolus injection (approximately 10 minutes, < 1ml) in the jugular vein at a dose of 7.5 mg B/kg (the dose was based on the study in mice) under ketamine-xylazine anesthesia. One group of 3 animals was sacrificed 2 hours post-administration and another group of 3 animals was sacrificed 3 hours post-administration. Samples of blood, tumor, precancerous tissue, normal pouch tissue, liver, spleen, kidney and lung were taken, weighed and processed by digestion in nitric acid for 1 hour at 100°C for measurement by ICP-OES. Additional normal tissues were stored for future measurement. In the case of tumor, given the characteristic spread in tumor boron concentration values, all available tissue was fractionated into 30–50 mg samples, processed and measured separately. No short-term toxicity was observed. At 2 hours post-administration, boron concentration values were: blood 21.4 ± 2.9 ppm (n=3); tumor 11.9 ± 4.0 ppm (n=11); precancerous tissue 7.2 ± 1.2 ppm (n=3); normal pouch tissue 6.8 ± 2.0 ppm (n=3); liver 32.8 ± 5.7 ppm (n=3); spleen 16.6 ± 4.0 ppm (n=3); kidney 18.2 ± 7.3 ppm (n=3) and lung 76.0 ± 16.5 ppm (n=2). No statistically significant differences were observed between boron concentration values at 2 and 3 hours post-administration. These results, albeit preliminary, are encouraging but strongly suggest the need to explore longer time-points post-administration of the boron compound to achieve preferential accumulation in tumor and clearance from blood, precancerous tissue and clinically relevant normal tissues that would be in the irradiation volume. Samples taken 5 hours post-administration in an additional group of hamsters are currently

stored for measurement as soon as we have access to our labs. Based on those results, additional time-points post-administration will be explored to assess the potential therapeutic value of Na[*o*-COSAN] as a boron carrier for BNCT in head and neck cancer. Follow-on BNCT studies at RA-3 Nuclear Reactor will be performed with Na[*o*-COSAN] enriched in ^{10}B.

Keywords:
BNCT, Na[*o*-COSAN], Metallacarboranes, head and neck cancer, hamster cheek pouch oral cancer model, boron compound, biodistribution study.

P50

Relationship of the abscopal effect to the survival rate after the head neutron-irradiation between the different types of mice

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INTRODUCTION: It is reported that immune response is activated by partial radiation. The influence on immune organization of the mouse at the time of the head irradiation is not well known. The purpose of this study is to evaluate the relative biological effectiveness in the severe combined immunodeficiency (SCID), so-called SCID mice, those have well-known high radiation sensitivity.

EXPERIMENTS: SCID mice were obtained from Charles River Inc. As a comparison experiment for the SCID mice, Balb/c and C3H/He mice were obtained from Japan Animal Inc.

Neutron irradiation and Gamma-ray irradiation was performed as follows. The Heavy Water Facility of the Kyoto University Research Reactor (KUR) was used. Mice were restrained in a plastic box on a radiation board. Neutron fluence was measured by radio-activation of gold foil and gamma-ray doses by TLD. Gamma rays were delivered with a ^{60}Co gamma-ray machine. Mice were restrained in a plastic box on a radiation shelf. The body of the mouse was covered with lithium as a neutron shielding plate. At 2 days after irradiation, apoptotic induction of the splenic cells was examined by Cell Death Detection ELISA.

RESULTS: RBE (Relative Biological Effectiveness) calculated from apoptosis of splenic cells following neutron radiation. RBE was calculated from the comparison of the enrichment factor at 3Gy neutron radiation dose and the enrichment factor at 3Gy gamma-ray radiation dose. The apoptotic induction of the splenocytes of SCID mice was larger than that of Balb/c and C3H mice at 2 days after irradiation. the RBE values of SCID mice was 1.57, comparing the neutron and the gamma studies. The RBE values of Balb/c and C3H/He mice was 2.09 and 2.28, respectively. The survival rate after the partial head-irradiation of the neutron, shows that 60% of the SCID mice died by partial neutron head-irradiation after 100 days and died all on the 356th day. On the other hand, the survival rate of Balb/c and C3H/He mice were 75% and 80% on the 356th day after neutron-radiation, respectively.

DISSCUSSION: The RBE values of SCID mice was 1.57, comparing the neutron and the gamma studies. The RBE values of Balb/c and C3H/He mice was 2.09 and 2.28, respectively. SCID mice show extreme sensitivity to ionizing radiation, because cells lack functional DNA-dependent protein kinase. Our results suggest that the difference of RBEs for radiation sensitive mice were smaller than the wild type mice, that is to say, the hyper radiation sensitivity does not have a disadvantage in BNCT. From the result of the survival study, 60% of the SCID mice died by partial neutron head-irradiation after 100 days. The partial head-radiation dose was about 1Gy that does not cause the bone- marrow death to SCID mouse. By the experiment of the acute radiation damage of the SCID mouse, the dose of $LD_{50/30}$ (the dose that 50% die within 30 days after radiation exposure) is reported around 4Gy. Because neutron sensitivity becomes higher, as for the SCID mouse that has inferior to a wildtype mouse in immunoreaction, partial neutron radiation works in the survival rate disadvantageously.

Boron-containing polymer micelles, SGB-complex, exhibit a combined antitumor effect of BNCR reaction and glycolytic inhibition.

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Recently, we have developed a unique water-soluble synthetic polymer that can form a stable complex with boric acid, i.e., a copoly (styrene-maleic acid) polymer-conjugated to glucosamine complexed with boric acid (SGB). The SGB- complex is rapidly taken up into tumor tissues and cells and releases free boric acid (BA) at the weakly acidic pH5-7 of tumor tissue and cytoplasm. This free BA competes with phosphoric acid in the phosphorylation of glucose, thus inhibiting the glycolytic system of the tumor and suppressing energy production (Warburg effect), thereby inhibiting tumor growth. In addition, SGB-complex showed the cytotoxic effect to tumor cells after under hypoxic conditions. Intravenous administration of the SGB complex at a dose of 15 mg/kg (boric acid equiv.) significantly inhibited tumor growth in S180 and C26 tumors, respectively, compared to the non-treated control group in which no toxicity was observed during the experimental period. In addition, it also showed a tumor-selective accumulation of SGB-complex is more than 10 times that of normal tissue. Furthermore, SGB-complex showed the remarkable antitumor effect with a dose of 10B, a few tenths of that of the existing boron compound BPA using SCCVII tumor-bearing mice. No significant changes in body weight or blood cells were observed, indicating that the treatment was safe. These results reveal at least two different mechanisms of anti-tumor effect: tumor suppression by BNCT and inhibition of glycolysis of tumor.

Keywords:
SGB-complex, polymer micelles, anti-tumor effect.

P130

Comparative studies in the use of Beta Enhancers devices as a complementary tool to BNCT for the treatment of cancer

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Introduction: The BNCT clinical trials in Argentina were restarted after changes in the beam in the RA-6 reactor. Due to the characteristics of the neutron beam, the maximum dose is not on the surface of the tumour, but at 1 cm depth. Some materials such as Rh, Ag and In have a high effective neutron capture section, rapid decay activation products and high energy beta particles emission. Since beta radiation has a short range of tissue penetration, these devices called Beta Enhancers (BE) can be used to compensate for the BNCT surface dose gradient or even to significantly increase it. In previous studies we showed its effectiveness in controlling tumour growth and increased cell damage and we demonstrated that three devices would be non-toxic and effective as complementary tools to BNCT for the treatment of superficial tumours (1). Several experimental studies of BNCT for tumours superficially implanted in the nude mice were performed and different parameters were followed up in order to evaluate the efficacy therapeutic of BNCT. Currently, the conception of cancer is that solid tumors have a complex cellular distribution within which appear cells with different proliferative capacity or different chemo and radio resistance (2). These cell populations that shares characteristics that makes them unique as a niche that maintains tumour survival are cancer stem cells (CSCs). It was proposed that CD133 could be a good marker of CSCs (3). Many therapies are not totally effective eliminating most of tumour cells and some tumours reappear. The new therapies should be targeted specifically against CSCs in an attempt to prevent resistance to them and tumor regeneration. So far there are no data linking BNCT therapy with CSCs, so it is useful to cover this study.

Objective: To evaluate the use of BE as a complementary tool in BNCT to the treatment of superficial tumors and to analyze the presence and persistence of CSCs after treatment.

Materials and Methods: NIH *nude* mice were implanted subcutaneously with HT29 colon cancer human line cells, developing tumors at day 15. There were two irradiations: In the first irradiation the animals were divided into 4 groups: Control; NCT; NCT + BE-Rh; BNCT and BNCT + BE-Rh. In the second irradiation the animals were divided into 5 groups: Control; BNCT + BE-Rh; BNCT + BE-Ag; BNCT + BE-In. Animals of groups 2, 3, 4 and 5 received 350 mg/kg of body weight of ^{10}BPA. The mice received subcutaneous anesthesia and were irradiated at a specific positioning for 37 minutes in first irradiation and 45.3 minutes in second irradiation with a neutron flux of 4.96×10^8 n/cm^{2}sec

Results: Animal monitoring after irradiation does not show any signs of radiotoxicity. Tumor growth curves were developed as a function of time, with a decrease in growth in all groups treated with the flakes, being less in groups with Rh. Histological studies had a correlation between the area of tumor necrosis and the total physical dose absorbed. A lower presence of cancer stem cells (CSC) was observed after three weeks of treatment.

Conclusions: All types of BE showed efficacy in controlling tumor growth post irradiation. Rhodium BE could causes greater tumor damage, however more studies are required to clarify the radiochemical processes

involved. Positive CSC populations are present in the Control group, and decrease in the first week after treatment in BNCT-BE groups and their persistence would be related to the tumor proliferation observed one month after treatment.

Keywords:
Beta enhancers, Cancer Stem Cells, CD133

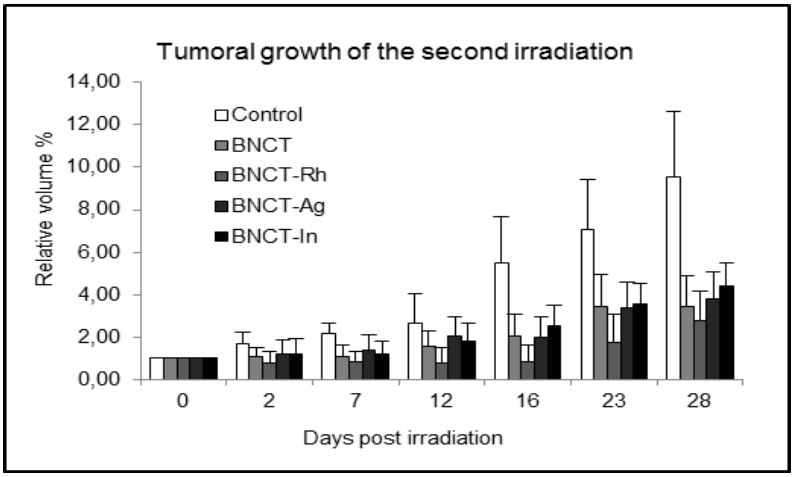

Figure 1: Tumor growth as a function of the time for each mice group in second irradiation

References:

(1) Boggio E. F. (2015). Beta Enhancers: towards a local dose enhancer device for Boron Neutron Capture Therapy (BNCT) on superficial tumors. IFMBE Proceedings. World Congress on Medical Physics and Biom, 51, 607-613.
(2) Krause M, A. D. (2017). Cancer stem cells: Radioresistance, prediction of radiotherapy outcome. Advanced Drug Delivery Reviews, 109 (2017) 63–73.
(3) O'Brien CA, P. A. (2007). A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature, 445 (7123): 106-110.

P134

Lamotrigine may increase *p*-boronophenylalanine uptake in human malignant meningioma cell lines by upregulating the expressions of amino acid transporters

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The efficacy of boron neutron capture therapy (BNCT) relies on the selective delivery of ^{10}B to malignant cells. The most important requirements for a boron delivery agent are: 1) low systemic toxicity and normal tissue uptake with high tumor uptake and concomitantly high tumor/brain and tumor/blood concentration ratios (>3-4: 1); 2) tumor concentrations of ~20μg B/g tumor; 3) rapid clearance from blood and normal tissues, and persistence in tumor during neutron irradiations; 4) possibility of mass producing with a low cost. Although many boron delivery agents have been proposed, only two compounds are currently under consideration in clinical trials, *p*-boronophenylalanine (BPA) and sodium borocaptate. The latter is an anionic polyhedral borane icosahedron containing 12 boron atoms. This compound is thought to enter tumor cells by passive diffusion through the plasma membrane. In contrast, BPA is localized to tumor cells by selective uptake mediated by amino acid transporters. Alterations of transporter expression in tumor cells, an adaption to altered tumor metabolism, offer opportunities for selective drug delivery. In this context, aromatic amino acid transporters upregulated in tumor cells are expected to play an important role in the delivery of BPA, a phenylalanine analogue.

Previous studies have suggested that system L transporters, particularly LAT1, are involved in the transport of BPA. The expression of LAT1 is highly upregulated in various cancers, where it is thought to contribute to tumor growth by increasing amino acids supply. It was previously demonstrated that expressions of LAT1 were upregulated by lamotrigine (LTG; one of the antiepileptic drugs). We show here that LTG may increase boron uptake in human malignant meningioma cell lines by upregulating them.

The in vivo relevance of LAT1 in pharmacokinetics is unclear, because contradictory findings have been reported. It is difficult to make quantitative pharmacokinetic conclusions about LAT1. Drug transporter interactions are common and were suggested to be relevant in the case of BPA transport, but in many cases the interactions that can be found in vitro are not significant for bioavailability in vivo.

In our study, a significant boron uptake in tumor cells was correlated with LTG, suggesting that LTG may play an role of drug interactions in boron uptake. The lack of direct correlation between the level of LAT1 expression and the boron uptake in our study may be due to interferences with other factors influencing boron uptake.

In conclusion, although our study showed that a positive boron uptake was associated with LTG concentration, we did not find a linear correlation between intensity of boron uptake and level of LAT1 expression. These results remain compatible with a role of LAT1 in boron uptake by malignant meningioma cells but suggest that LAT1 expression alone is not sufficient to explain variation of intensity of boron uptake in malignant meningioma. These should be confirmed in a larger and more homogeneous series of tumors in the light of other potential

factors influencing boron uptake. This is a preliminary study suggesting that antiepileptic drugs, which are commonly used in patients with brain tumors, may have an interaction with BPA. Although the difference is minor, it needs to be examined whether it is negligible or not.

Keywords:
here your keywords
amino acid transporter, antiepileptic drug, *p*-boronophenylalanine, Lamotrigine

P150

The PICTURE project: toward biological dose prediction of targeted radiotherapies emitting short-range ions

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PICTURE is a highly pluridisciplinary project aiming at optimizing and improving predictions of the biological effects of targeted radiotherapies (RTs) emitting short-range ions, such as targeted-radionuclide therapies (TRT) with alpha-emitters and boron neutron capture therapy (BNCT). Indeed, alpha-TRT and BNCT raised a growing interest to treat diffuse and aggressive cancerous tumors thanks to, respectively, the fast development of radioimmunotherapy and of epithermal neutron sources based on accelerators. Like in ion-beam therapy, treatment planning of such therapies requires biological dose estimation as soon as high-LET ions are emitted by the radio-emitters (i.e. low-energy protons, alpha and lithium ions). Due to the short range of few micrometers of these ions, one expects that the microdistribution of radio-emitters and the geometry of cell impact the biological dose. It is therefore of utmost importance to consider extra-nuclear sensitive volumes in particular when radio-emitters are located outside the cell nucleus. At the moment, the cell nucleus is the only sensitive volume considered in biophysical models able to predict biological dose in ion-beam therapy. One of such models, NanOx [1,2], has been recently developed and shows good predictive performances of cell survival in hadrontherapy applications. Its design enabling convenient implementation of new mechanisms and an easy coupling with Monte-Carlo tools like G4-DNA, makes it a nice tool to address the modeling of biological dose for targeting RTs. The extension of the NanOx model, including the consideration of extra-nuclear sensitive sites, will lead to the introduction of new biological parameters that will be determined by means of innovative techniques.

We intend in the PICTURE project: first, to evaluate the impact on cell death of the spatial alpha-emitter or boron distribution at the cellular scale using Monte-Carlo based simulations with GATE/Geant4-DNA codes, with implemented realistic microscopy-based cell geometry, and the current version of the NanOx model ; Then, to adapt the NanOx model to cell-survival predictions at very low-energy ions (still using only the cell nucleus as sensitive site) performing specific biological experiments with low-energy proton, alpha and lithium ion beams ; And finally, to extend the NanOx model to consider two sensitive sites (i.e. the nucleus and the extra-nuclear (cytoplasm and membrane) parts of the cell) in the quantification of damage, based on extensive simulation studies and dedicated biological experiments.

A global description of the aims and methods planned in the PICTURE project will be presented, as well as the first calculation results, related to BNCT, available at the time of the conference.

Keywords:
BNCT, Monte Carlo simulations, biophysical models, NanOx, radiobiology.

References:

[1] Monini, C., Alphonse, G., Rodriguez-Lafrasse, C., Testa, É., & Beuve, M. (2019). Comparison of biophysical models with experimental data for three cell lines in response to irradiation with monoenergetic ions. Physics and Imaging in Radiation Oncology, 12, 17-21.

[2] Cunha, M., Monini, C., Testa, E., & Beuve, M. (2017). NanOx, a new model to predict cell survival in the context of particle therapy. Physics in Medicine & Biology, 62(4), 1248.

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Biological evaluation of the accelerator-based BNCT system in National Cancer Center Hospital

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Accelerator-based BNCT system with lithium target has been installed in National Cancer Center hospital in Japan. We have evaluated the physical characteristics and relative biological effectiveness (RBE) of the neutron beam using cells and mice.

We have used human cancer cell lines including SAS, A375, MeWo and HSG, and C57BL/6J mice. Irradiation of neutron or gamma-ray was performed with/without boron compounds with therapeutic doses of BNCT. We performed colony formation assay to evaluate the RBE for neutron free-beam irradiation condition. The RBEs were in the similar ranges compared with previous reports. Next, we performed colony formation assay and micronuclei test to check damages. The cell survivals and the frequency of micronuclei were dose-dependently decreased after neutron beam irradiation. Then, C57BL/6J mice were used to assess the biological effectiveness of neutron beam irradiation. Total body irradiation and local irradiation to legs were performed, and skin damages and the numbers of white blood cells (WBCs) were measured. For the local irradiation, mice body were covered by shields containing 6-Li. The significant skin damage was not detectable in all groups. The numbers of WBCs in neutron beam irradiated group showed a decrease on day 7, although the recovery was observed to the level of control group on the day 40. These results suggests that the BNCT system showed a significant cell killing effects, and the therapeutic dose irradiation of neutron did not cause fatal damage to the skin and WBCs in mice experiment.

Keywords:
Preclinical experiment, RBE

Boron determination and imaging

Boron determination and imaging

Boron determination and imaging

Towards 10B dosimetry: a multi-energy line detector for BNCT-SPECT

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Introduction: First clinical trials for the new accelerator-based boron neutron capture therapy (AB-BNCT) facilities have started, which raises the need of real-time ^{10}B dosimetry during the therapy to higher priority. ^{10}B dosimetry information can also be used for imaging and localization efforts, which are referred to as BNCT-single photon emission computed tomography (BNCT-SPECT). Both dosimetry and imaging tasks employ the signal from the $^{10}B(n,a)^{7}Li^{*}$ (BNC) reaction in the tumor. Detectors require at minimum an energy resolution of ~16.5keV at 511keV, a spatial resolution of <1cm and a capability to work in high flux conditions, to be used for BNCT-SPECT. Cd(Zn)Te detectors have the potential to fulfill these requirements. In this study we have tested a prototype of a CdTe line detector for BNCT-SPECT these requirements.

Materials and Methods: The detector is a prototype is based on the multi-energy X-Card ME3 detector module from Detection Technology. The line detector consists 128 pixels of 0.8 mm size, each pixel acquires spectra with up to 256 energy bins and the detector sensitivity is verified up to 1MeV. Furthermore, up to 12 modules can be daisy chained to create a line-detector of 1.2 m. A single detector module was tested at the accelerator-based neutron facility C-BENS in Kyoto. A cylindrical acrylic phantom filled with water was used. The phantom contained a target capsule with boric acid of 2100ppm ^{10}B concentration. The phantom was rotated to 8 positions of which one was in direct view of the line-detector. The detector was positioned in parallel to the beam and phantom axis. A low neutron flux of $10^{8}/cm^{2}s$ (<10% accelerator current) was employed and the detector was shielded with a 10 cm of Li-plastic collimator. The collimator allowed to leave the active area of the detector unshielded. The whole experiment was also simulated in PHITS version 3.02, for which the JENDL4.0 and TENDL2008 libraries were used.

Results: The simulation results indicate that the detector should detect the presence of the capsule, if it is located in front of the detector. This was confirmed through the measurements. We could also confirm that the detector has an energy resolution of 13 keV at 511 keV for every pixel. Furthermore, the simultaneous detection of the BNC and $^{113}Cd(n,g)^{114}Cd^{*}$ (CdNC) reaction signals were confirmed. The later behaves inverse to the BNC reaction. However, a limitation of the prototype became also eminent, as heavy pile-up effects and radiation induced software errors were noted.

Conclusion: A prototype based on the X-Card ME3 detector module proved to be principally sufficient for BNCT-SPECT in terms of spatial and energy resolution. However, pile-up effects and radiation hardness are topics for further development. Nonetheless, the prototype could already be used for low (neutron) flux imaging applications, such as boron drug tests or technical evaluations.

Acknowledgments:
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Improvements in design of prompt gamma facility for BNCT at RA-3: on the verge of the desired detection limit

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Prompt Gamma Neutron Activation Analysis (PGNAA) is a technique that can be used for measuring ^{10}B concentrations in biological samples for different BNCT activities. This method is based in measuring the 478 keV prompt gamma emissions after thermal neutron capture in boron, which occurs the 94% of the cases. The main two advantages of this macroscopic technique are that it does not require to pretreat the sample and can provide results in few minutes. In the frame of BNCT activities, a PGNAA facility is being developed in the channel 4 of RA-3 10 MW nuclear reactor by the Argentine National Atomic Energy Commission (CNEA). The design goal of this facility is being able to perform fast measurements of small biological samples containing micrograms of ^{10}B. Such conditions are very important for BNCT research, development and clinic-related assessments.

In order to reach the aim of the facility based on BNCT sample requirements, different stages of design have been performed. Initially, a feasibility study for the assessment of the reactor channel for neutron beam requirements was conducted. With the satisfactory results, an irradiation device coupled with the channel 4 had been designed and constructed in the reactor hall. After that, an iterative simulation guided design process along with progressive construction and experimental measurements, lead to an adequation of the extracted neutron beam. A measured thermal neutron flux at sample position of $3 \cdot 10^7$ n/cm^2·s and 2.5 cm of diameter had been achieved, with epithermal and fast neutron components around 4 orders of magnitude lower. The sample position is inside the irradiation device, at 5.2 m from the core's center. A high purity germanium detector is positioned perpendicular to the neutron beam line, at 40 cm from the sample position. Following that stage, the gamma background had been significantly reduced in the detector region and a detection limit of 1.2 µg of ^{10}B had been experimentally achieved in boron powder samples without matrix. For samples of boric acid with matrix of 250 µl ultrapure water, that would behave similar to biologic tissue, a detection limit of 3.2 ppm, was also experimentally reached.

After these experiments, and looking for the improvement in detection limit, an assessment of the design was performed in order to keep reducing the gamma background in the detector region. For this, neutron and photon transport was analyzed by regions, identifying those areas of the facility that have greater impact mainly in the detector background spectrum. Once these areas have been identified, several components have been designed, tried and evaluated with MCNP6, in order to shield neutron and/or photon particles accordingly. The conceptual shielding components that provided the best performances, have been identified and added gradually in the design, being able to obtain significant reductions in gamma background step by step. The simulations with the best of the proposed shielding components set, were implemented in the numerical design and have shown a detection limit of ~0.1 µg of ^{10}B for samples without matrix. Simultaneously, reductions of 95% and 92% in the

total gamma and neutron background respectively at the detector position, have been achieved compared to the current implemented facility.

The performance of new conceptual components of the facility has been evaluated through Monte Carlo simulations, and proved to efficiently shield neutrons and photons that, otherwise, would eventually travel to the detection region. As a result, a significant improvement of the detection limit of ^{10}B has been achieved and the obtained value would match the initial aim of the design of the facility. These proposed modifications will be gradually implemented and measured in the facility, when presential work can be performed.

Keywords:
prompt gamma, boron measurement, spectrometry, MCNP, biological sample.

An experimental verification for the discrimination-ability between tumor and normal parts using the improved gamma-ray telescope system

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INTRODUCTION: It is important to decide the boron concentrations for tumor and normal parts in the dose estimation for 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) [1,2]. 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-filed of the telescope can be expanded or reduced by moving the two collimators independently.

The experimental verification was performed for the discrimination-ability between tumor and normal parts using this telescope system.

MATERIALS AND METHODS: A liquid rectangular phantom of 20 cm in width, 20 cm in length and 40 cm in depth was used in the experiment. An acrylic hollow sphere of 5 cm in outer diameter, which was filled with boric acid of 193 ppm for B-10 concentration, was placed as a tumor part in the phantom. The phantom liquid was pure water or boric-acid water of 23 ppm for B-10 concentration. The epi-thermal neutron irradiation was performed in the irradiation field of 12 cm in diameter. The initial position of the tumor-sphere center was settled to be the center for the telescope-view-field on the beam axis, and it was moved from 0 to 6 cm in the right direction for the view from the beam-aperture side.

The positions of two telescope collimators were fixed to be the lowest. At these positions, the effective telescope-view-field on the beam axis was within 3 cm in width in the right direction for the view from the beam-aperture side. The prompt gamma rays due to the neutron reactions with B-10 and hydrogen (H-1) from the tumor part and its surroundings during the epi-thermal neutron irradiation were counted.

RESULTS AND DISCUSSION: Figure 1 shows the relationship between the position of the tumor-sphere center and the count ratio for B-10 gamma rays to H-1 gamma rays (B/H count ratio). It was confirmed that the B/H count ratio was larger as the position of the tumor-sphere center was closer to the beam axis, namely as it was closer to the center of the effective telescope-view-field. It was also confirmed that the B/H count ratio was larger for the boron-acid water phantom than for the pure water phantom. It is because that the B-10 gamma rays from the boric-acid water of 23 ppm for B-10 concentration in the telescope view-field additionally contribute to the B-10 gamma-ray count.

CONCLUSION: The B-10 concentration ratio for the tumor sphere to the boron-acid water phantom was 8.4 in this experiment. For such a level of the concentration ratio, the discrimination between tumor and normal parts

can be expected by comparing the count ratio between the cases with and without the tumor part in the telescope view-field. In the actual BNCT clinical study, the B-10 concentration of the normal part is 10 to 25 ppm, and that of the tumor part is more than three times larger. In future, 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.

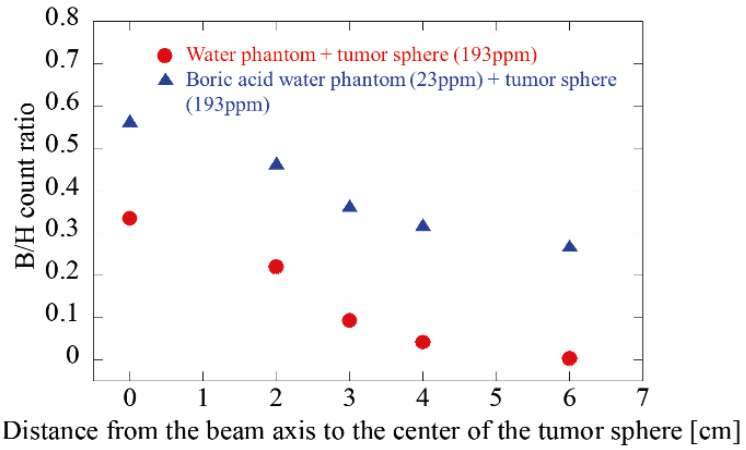

Figure 1. *Relationship between the center position of the tumor sphere and the B/H count ratio.*

Keywords:
gamma-ray telescope, prompt gamma-ray analysis, boron-10 concentration, on-line estimation, real-time estimation

Referencia:

[1] Y. Sakurai et al., Appl. Radiat. Isot. 61 (2004) 829-833.
[2] Y. Sakurai et al., Appl. Radiat. Isot. 165 (2020) 109256.

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Towards the optimization of BNCT dosimetry in lung: boron macro and microdistribution studies in normal sheep

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The multiinstitutional Argentine project "Therapeutic Potential of BNCT for the Treatment of Multiple Lung Metastases: Feasibility and therapeutic efficacy study at an experimental level of a novel *ex-vivo* irradiation protocol" has two main objectives: to study the radiotoxicity in a sheep model of normal lung and to assess the therapeutic efficacy in an experimental model of colon carcinoma diffuse lung metastases in BDIX rats.

In this context, the validity of the ovine model as an adequate human surrogate in terms of boron kinetics in clinically relevant tissues was established [1]. A phantom of a collapsed human lung was constructed and used for computational dosimetry assessments. From simulations of the organ irradiation inside the thermal column of a nuclear reactor and a suitable tumor control probability (TCP) model for lung cancer, a promising average fraction of controlled lesions was obtained. The therapeutic efficacy of BNCT was demonstrated in the small animal cancer model [2]. Recently, the neutron autoradiography technique was extended to study the boron microdistribution in normal and metastatic lung from BDIX rats [3].

The *ex-situ* procedure consists in boron infusion, irradiation of an explanted organ followed by surgical reimplant in the sheep. This process requires perfusion of the organ with a preservation solution. In the last years, optimizations to the preservation protocols were proposed. The aim of the present work is to evaluate if these modifications impact on the boron concentration at a macroscopic level. Moreover, we seek to apply the autoradiography technique to samples coming from sheep lung. The final aim is to contribute to an optimization of the dosimetry in a clinical scenario.

A new boron biodistribution study of a normal sheep was performed, infusing boronophenylalanine-fructose (350mg/kg) for 40 min. Under anesthesia, samples of lung (L), blood (B), skin and muscle were extracted for boron determination. The left lung was removed after 1h of infusion start. The perfusion procedure was performed in a container with ice, to maintain the temperature around 4°C. The perfused organ was sectioned following a grid and conserved for neutron autoradiography and ICP-OES measurements. The same procedure was repeated for the right lung and the animal was euthanized.

Boron concentration-time profiles for left lung prior to perfusion, skin and blood were fitted using a two-compartment model and the ICP-OES measurements. Also, a distribution of the boron retention factor (RF) after perfusion was obtained and compared with previous results. Thin sections of normal lung were mounted on polycarbonate films and the assembly was irradiated and processed to obtain qualitative autoradiographic images. Moreover, the reanalysis of the data provided by quantitative neutron autoradiography on the BDIX rat model yielded a distribution of Tumor/Blood ratios from 42 individual tumors (T). The collective results of the macro and

microdistribution studies in normal sheep (including RF) and rats were used to feed the analysis in the clinical-like scenario for humans. The standard model with RBE and CBE factors from [4] for normal rats was used to compute the dose in Gy-Eq.

Both the boron kinetics and the RF showed consistency with previous studies. A non-uniform distribution of boron was observed in the sheep lung after the perfusion process, at macroscopic level (mean RF: 0.3±0.1). The distribution of T/B ratios of individual tumors from BDIX rats showed a lognormal behavior (mean: 1.6±0.2). The dosimetric analysis allowed to estimate the TCP in an irradiated explanted lung with multiple nodes uniformly distributed. For a T/L ratio of 2.1±0.3 and limiting the mean lung dose to 7.5Gy, the percentage of controlled lesions is over 80%. At the microscopic level, a preferential uptake of BPA in the broncho-vascular tree was observed (Figure 1). This way, boron microdistribution in normal sheep lung was assessed for the first time. Ongoing studies seek to quantify boron distribution in these structures, as they could explain potential vascular damage in normal lung after BNCT.

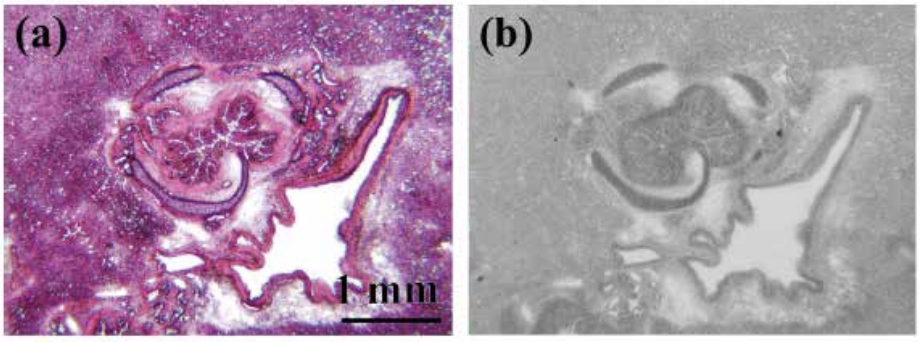

Figure 1. Normal lung section (30µm) of a sheep after the infusion with BPA and the perfusion process. (a) H&E, (b) autoradiographic image (2.5x). 10^{13} ncm^{-2}, KOH, 70°C, 4min.

Keywords:
lung; microdistribution; ICP-OES; *ex-situ* irradiation; pharmacokinetics; neutron autoradiography

Acknowledgements:
The authors are grateful to Prof.Dr. Mariel Itoiz for expert advice in histological analysis.

References:

[1] Farías et al.,Med Phys 42,4161-4173,2015.
[2] Trivillin et al.,Int J Radiat Biol 95,646-654(2019)
[3] Espain et al.,ARI 165,109331(2020)
[4] Kiger et al., Radiat Res 170, 60-69(2008)

Performance study of a cadmium–zinc–telluride drift strip detectors in a mixed thermal neutron - gamma field

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The in vivo measurement of the dose in a BNCT treatment still remains a great challenge; various groups in the world are developing imaging techniques that are able to measure online the contribution from the reaction $^{10}B(n,\alpha)^{7}Li$ with techniques such as SPECT or Compton Camera using the 478 keV photon emitted by the excited ^{7}Li [1].

Since few years, a research in this field started at Pavia University and Pavia INFN Unit focusing on solid state CdZnTe (CZT) photon detectors that present several advantages: high atomic number (leading to high detection efficiency using relatively small sensitive volumes), wide band gap which allows room temperature operation without the necessity of bulky cryogenic systems, very good energy resolutions in a wide energy range for highly performing spectrometry, possibility to realize customized pixel/strip electrodes by standard photolithography to obtain high spatial resolution imaging detectors [2].

Recently, at the Triga Mark II reactor of the Applied Nuclear Energy Laboratory (LENA) of Pavia University, a collimated thermal neutron beam has been realised, offering the possibility to perform PGNAA measurements, neutron imaging and to test various types of detectors, including the named CZT technology for BNCT dose monitoring application.

A 20 mm x 5 mm x 5 mm CZT drift strip detector with one single read-out anode strip and a full area cathode was used to carry out a campaign of measurements to study its response to 478 keV photons in a mixed gamma and neutron radiation environment similar to that found in a BNCT treatment room, i.e. the one available at the named PGNAA facility. These measurements represent a preliminary step to understand the best possible measuring postitions inside the Pavia PGNAA facility to carry out other experiment involving more performing CZT detectors presently under development and characterization, i.e.: 3D drift strip detectors for spectro-imaging and Compton Camera and Frish grid sensors for SPECT imaging.

The talk will present the results of these measures and the future steps of the described researches.

Keywords:
CdZnTe detectors; drift strip detectors, Frish grid detectors, SPECT, Compton Camera

References:

[1] T. Kobayashi, Y. Sakurai, e M. Ishikawa, «A noninvasive dose estimation system for clinical BNCT based on PG-SPECT-Conceptual study and fundamental experiments using HPGe and CdTe semiconductor detectors», Med. Phys., vol. 27, n. 9, pagg. 2124–2132, set. 2000, doi: 10.1118/1.1288243.
[2] S. Del Sordo, L. Abbene, E. Caroli, A. M. Mancini, A. Zappettini, e P. Ubertini, «Progress in the Development of CdTe and CdZnTe Semiconductor Radiation Detectors for Astrophysical and Medical Applications», Sensors, vol. 9, n. 5, pagg. 3491–3526, mag. 2009, doi: 10.3390/s90503491.
[3] L. Giuntini et al. Detectors and Cultural Heritage: The INFN-CHNet Experience Appl. Sci. 2021, 11, 3462. https://doi.org/10.3390/app11083462.

Boron determination and imaging

Poster

Comparison of CR-39 autoradiography and laser ablation ICP-MS imaging to assess ^{10}B distribution of tibia bone in ^{10}BPA-treated mice

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In an animal study for developing boron neutron capture therapy, it is important to know the ^{10}B bio-distribution of the after administered ^{10}B-formula. To reveal the ^{10}B bio-distribution in the body, autoradiography with CR-39 is a useful bioimaging method [1]. To perform autoradiography, neutrons must be irradiated, which limits the location and facilities where it can be performed. At the same time, the combination of the laser-sampling and inductively coupled plasma-mass spectrometry (LA-ICP-MS) technique is also known a useful analytical tool for biological imaging of elements. Since ICP-MS can analyze elements by their mass-to-charge ratio, it is thought to be useful for bio-imaging of ^{10}B, as well as autoradiography, without being affected by ^{11}B, an isotope of boron [2]. In this study, the distribution of ^{10}B in the tibia bone of mice treated with ^{10}BPA was measured by CR-39 autoradiography and LA-ICP-MS for comparison. C3H/He female mice (8 weeks old) were obtained from Japan SLC, Inc. (Shizuoka, Japan). ^{10}BPA were injected subcutaneously into nuchal sites at a concentration of 125, 250, or 500 mg/kg. After 1 h of injection, mice were sacrificed and tibia bone were sampled. For each mouse, the right tibia bone was cut into thin sections every 5 µm using the Kawamoto method, a non-demineralized frozen section preparation method, and the ^{10}B distribution was determined by both CR-39 autoradiography and LA-ICP-MS technique. The ^{10}B in tibia imaged both techniques showed similar distribution. The semi-quantitative concentration results of ^{10}B in the growth cartilage, where ^{10}B was the most concentrated, was calculated to be about 40 ppm by CR-39 technique and about 80 ppm by LA-ICP-MS technique, which was of similar order. Although LA-ICP-MS bioimaging was not reveal the distribution of ^{10}B with as high resolution as CR-39 autoradiography, it was effective for clarifying the bio-distribution of ^{10}B before the administration of ^{10}B-formula.

Keywords:
CR-39 autoradiography, laser ablation ICP-MS

References:

[1] Ogura, K., et al. Radiation measurements 34.1-6 (2001): 555-558.
[2] Tsurubuchi, T., et al. Cells 9.5 (2020): 1277.

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Experimental Examination for Cross-talk Phenomena in BNCT-SPECT

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Recently, Boron Neutron Capture Therapy (BNCT) attracts attention as a new radiation therapy for cancer. However, BNCT has some problems unsolved to establish. One of them is that the local dose cannot be known during irradiation in real time. Thus, we have been developing a SPECT system for BNCT, so-called BNCT-SPECT, which can obtain a three-dimensional image of local boron dose to monitor the treatment effect around the tumor cells in real time. The principle is to measure 478 keV gamma-rays emitted promptly from the excited state of ^{7}Li produced by the ^{10}B(n,α)^{7}Li reaction. In our research group, a GAGG(Ce) scintillator is used as the elemental device.

Previously our group designed our own BNCT-SPECT system using only one detector. However, the point is that it is difficult to selectively measure the 478 keV gamma-rays, which represent the treatment effect. This is because the primary radiation is neutron in BNCT and gamma-rays to be measured is just a small part of the secondary radiations, which contains a large amount of background noises. In this study, we investigated a method to reduce the background noise existing in the BNCT treatment site in order finally to improve the statistical accuracy of the 478 keV gamma-ray.

To solve this problem, we examined possibility of noise reduction by anti-coincidence or coincidence detection using so-called cross-talk phenomena. Anti-coincidence and coincidence detections are a type of radiation measurement method. And the cross-talk phenomena can occur when multiple detectors are arranged like a SPECT machine and multiple gamma rays are measured simultaneously by multiple detectors.

Proceeding with experiments and simulations by PHITS (Monte Carlo particle transport code) based on the above considerations, a simple experimental system with just two detectors was made and the behavior of cross-talk phenomena was experimentally investigated. After that, we evaluated possibility of the noise reduction by anti-coincidence or coincidence detection.

As a result of measurement using a Cs-137 source (661.2 keV), cross-talk phenomena were observed. Since experimental and calculated results by PHITS showed almost the same, PHITS was validated to be used for the cross-talk analysis. Also, calculated results showed that the noise could successfully be reduced by 15.9 % in coincidence detection and 3.8 % in anti-coincidence detection compared to without noise reduction.

From the present study, it was confirmed that the noise could be reduced successfully, and the statistical accuracy could consequently be improved by anti-coincidence or coincidence detection in BNCT-SPECT system.

In the next step, the effect of noise reduction by increasing the number of detectors up to the real BNCT-SPECT machine will be examined, then finally, we will produce the real BNCT-SPECT machine.

Keywords:
BNCT-SPECT, cross-talk phenomena, anti-coincidence detection, coincidence detection

Comparison of SUV in blood pools using FBPA PET and blood boron concentrations in BNCT

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[Objective]

To compare the SUV values of the blood pool on FBPA PET performed at a dose based on body weight with the boron-10 (^{10}B) concentration in the blood after administration of the therapeutic dose of BPA at the time of BNCT.

[Subjects and Methods]

Sixteen patients with advanced or recurrent head and neck tumors (male/female, 11/5; mean age 69 years, ranging from 43 to 89 years) who underwent FBPA PET scan to investigate the applicability of BNCT, and later were determined to be eligible and underwent BNCT were included in the study. Whole-body scan was performed using a PET/CT system, with the scan starting from 60 minutes after intravenous administration of FBPA at a dose based on body weight. ^{10}B concentration in the blood was measured using ICP-OES after administration of therapeutic doses of BPA during BNCT.

[Results]

The mean SUV value of the blood pool was 1.2±0.2; the mean blood ^{10}B concentration during BNCT was 18.3±2.9 ppm at 1 hour, 28.3±4.8 ppm at 2 hours, and 27.0±3.1 ppm immediately after treatment. There was no correlation between SUV values in the FBPA PET blood pool and blood ^{10}B concentrations during BNCT.

[Discussion]

We speculate that the reason for the lack of correlation between the two may be that FBPA (an amino acid analogue) has low accumulation in fat and that the dose per body weight did not provide a significant correlation. We are currently conducting a study to investigate the possibility of correcting for non-fat body weight.

[Conclusion]

There are limitations in accurately estimating blood ^{10}B concentrations after administration of therapeutic doses of BPA during BNCT from SUV values in the blood pool of FBPA PET performed at doses based solely on body weight.

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Improvement of quantitative autoradiography in boron neutron capture therapy.

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Boron neutron capture therapy (BNCT) is a cellular-scale particle therapy exploiting boron neutron capture reactions in boron compounds distributed in tumour cells. Its therapeutic effect depends on both the accumulation of boron in tumour cells and the neutron fluence. Autoradiography is widely used to quantitatively visualize the microdistribution of boron compounds. However, in the process of autoradiography, the condition of the tissue section is different from that in vivo. Hence the particle ranges of alpha particles and recoiled lithium nuclei are varied from these in vivo. In the quantitative analysis using autoradiography, it is necessary to take it into account. Here, we present an equation for the relationship between boron concentration and pit density on the solid-state nuclear track detector, taking into consideration the particle ranges in the samples. This equation provides a theoretical explanation for the widely used calibration curve between pit density and boron concentration; it also provides a method to correct for differences in tissue-section thickness in quantitative autoradiography. In this study, the equation was validated using liver-tissue sections and boron standard solutions. Autoradiography was performed using liver tissue sections from BPA-administered mice (boron concentration was measured by inductively coupled plasma - atomic emission spectrometry) and boron standard solution, and the relationship between boron concentration and pit density in autoradiography was measured and compared with the calculated value using the equation. In addition, the thickness of the tissue sections of the liver was varied to compare the measured and calculated pit density. This study reproduced the experimentally observed trends between boron concentration and pit density. Using this equation could improve micro-scale quantitative estimation in tissue sections, and it is expected to provide new insights into the microdosimetry in BNCT.

Keywords:
Autoradiography, Boron Microdistribution

Dosimetry and treatment planning

Dosimetry and treatment planning

Dosimetry and treatment planning

Measurement of thermal neutrons and gamma rays using MAGAT-type gel detector doped with LiCl for BNCT at Kyoto University Reactor.

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The quality assurance (QA) of an irradiation field can be performed by monitoring the spatial beam component distributions in a phantom for boron neutron capture therapy (BNCT). Ideally, the beam components are measured separately, e.g., thermal neutrons (-0.5eV), epithermal neutrons (0.5eV-10keV), fast neutrons (10keV-), and gamma rays. A good candidate detector for spatial distribution measurements are a gel detector [1] which have been used in three-dimensional dose distribution measurement for photons and heavy ion irradiations. In a related study, we have demonstrated that gel detectors can separately measure the relative fluence of the components of a BNCT neutron field [2]. We found from Monte Carlo calculations that the MAGAT-type polymer gel detector doped with ^{6}Li at concentrations of 0, 10 and 100 ppm are potentially usable for thermal and fast neutrons, and gamma ray measurements. The components were attempted to be measured by increasing the sensitivity of the gel detector to the fast neutron component via recoil protons and increasing the sensitivity to the thermal neutron component via the secondary particles from the ^{6}Li(n,α)^{3}H reaction. The gamma ray component of the beam deposits its energy mainly via secondary electrons. The present paper describes an experimental demonstration of these measurements using the gel detectors.

The MAGAT-type gel detector was infused with LiCl, where the naturally abundant isotope ^{6}Li was used. The ^{6}Li concentrations were set at 0, 10 and 100 ppm. The dimension of the gel detector was 60 × 60 × 60 mm^{3}. The box was set inside a 200 × 200 × 200 mm^{3} acrylic acid resin phantom. During the irradiation, the box was placed in contact with the collimator aperture of the Kyoto University Reactor Heavy Water Neutron Irradiation Facility (KUR-HWNIF) [3]. The irradiation was performed with the standard epithermal neutron irradiation mode at 1 MW delivered for 110 minutes for 0 ppm, 60 minutes for 10 ppm, and 30 minutes for 100 ppm. The nominal value of the flux was 7.07×10^{6} cm^{-2}s^{-1}, 1.33×10^{8} cm^{-2}s^{-1} and 1.38×10^{7} cm^{-2}s^{-1} for thermal, epithermal and fast neutrons, respectively. The gamma ray flux was 1.25×10^{7} cm^{-2}s^{-1}. After the irradiation, the transverse relaxation rate was measured as the signal intensity of the gel detector, by using a 0.3T MRI scanner (AIRIS II comfort, Hitachi Medical Corp.). Here, *i* indicates the ^{6}Li concentration in the gel detector wherein 1, 2 and 3 denote 0, 10, and 100 ppm, respectively.

As a result, the fluence distribution measured by the gel detector agrees to within 20% to 30% of other estimates such as gold activation for thermal neutrons and thermoluminescence dosimeter for gamma rays. This suggests the potential usability of polymer gel detector in spatial measurement of fluence in BNCT beam.

As a summary, a trial to measure the spatial distribution of the neutrons, depending on their energy, and gamma rays separately was carried out by using the MAGAT-type gel detector infused with LiCl. Potential

usability of the gel detector was shown for two components, i.e., thermal neutrons and gamma rays, for which the obtained fluence distributions agreed with those estimated by conventional methods.

Keywords:
BNCT, Gel, beam component, quality assurance

Reference:

[1] De Deene Y and Vandecasteele J 2013 *J. Phys. Conference Series* **444** 012015
[2] Tanaka K, Sakurai Y, Hayashi S, Kajimoto T, Uchida R, Tanaka H, Takata T, Bengua G and Endo S. 2017 *Appl. Rad. Isot.* **127** 253-259
[3] Sakurai Y and Kobayashi T 2000 *Nucl. Instr. Meth.* **A453** 569-596

Personalized Three Dimensional Dose Prediction of BNCT Based on CT and Neural Network

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Boron neutron capture therapy (BNCT) is a binary radiotherapy based on the $^{10}B(n,a)^{7}Li$ capture reaction, it has become an innovative technology in radiation therapy because of its targeted treatment, low toxicity and high efficiency[1]. In clinical, an appropriate treatment plan needs to be set based on treatment planning system(TPS). The existing BNCT TPSs all use the Monte Carlo method to simulate the therapeutic dose distribution, which often requires a lot of calculation time due to the complexity of simulating neutron transportation[2].

In order to solve this critical problem, a novel method for predicting 3D therapeutic dose based on neural network is proposed, and the feasibility is demonstrated. The principle of the method proposed in this study is to construct the relationship between the CT image of the patient and the therapeutic dose through neural network. Generative adversarial networks (GAN) architecture is selected to predict 3D therapeutic dose distribution from 3D-CT image[3]. Sixteen cases with glioma are used as the training set, two cases are used as the validation set and two cases are used as the test set. The dataset with the information of CT contour, boron concentration distribution and irradiation field are feed in the GAN to generate the images of therapeutic dose distribution, as shown in Fig1 a). In this study, the irradiation geometry of top to bottom is adopted, and the MIT epithermal neutron beam is selected. Ten types of organs are concerned, as shown in Fig1 b).

The predicted results with personalized patient geometry and specific boron concentration are analyzed. The dose volume histograms for tumor and normal tissues of the test case are shown in Fig1 c). Analysis of the performance of the method shows that the method has excellent generalization. For individualized cases, the dose volume histograms (DVH) for tumor are in good agreement with the simulated results, as shown in Fig1 d). Taking the dose to 95% of the tumor volume (D95) as an example, for different boron concentrations, the relative deviation between the predicted results and the simulated results are all less than 4%, as shown in Fig1 e). For the boron concentration which does not exist in the training sample, the prediction results are also in good agreement with the simulation results, and the relative deviations are less than 8%. For the calculation time, it takes about 5 hours to simulate the dose distribution of a patient (i.e., using 85 threads), while the time required by this method is less than 2 seconds (i.e., using Titan-V graphics card). This result shows the great cost-effective advantage of the method proposed in this study. In the future, we will increase the sample data to further improve the accuracy of the method, so as to promote its clinical application.

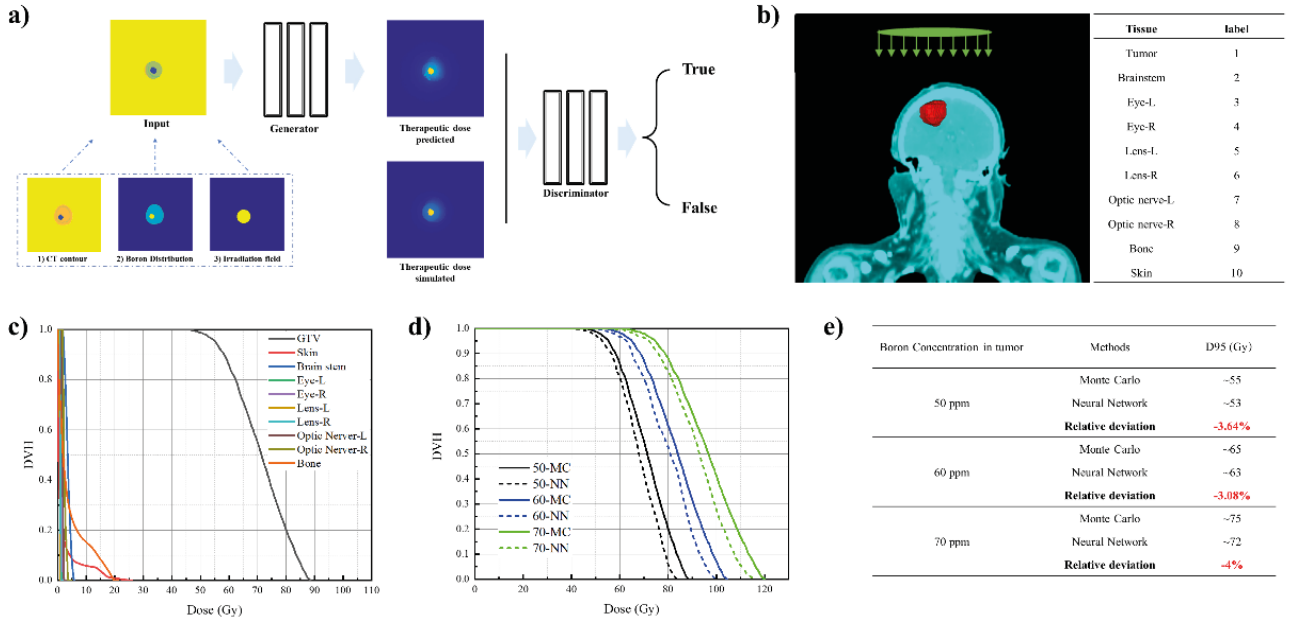

Figure 1. a) The configuration of GAN using in this study. b) A case of male glioma patients and the tissues selected in this study. c) DVHs for tumor and organs when the max dose of skin is 26 Gy. d) DVHs for tumor with different boron concentration between Monte Carlo simulation and predicted by neural network. e) The relative deviation of D95 between Monte Carlo simulation and predicted by neural network.

Keywords:

BNCT; CT; Therapeutic dose; Generative adversarial networks.

References:

[1] Tian F, Geng C R, Tang X B, et al. Nuclear Science and Techniques, 2021, 32(4): 1-10.
[2] Takada K, Kumada H, Matsumura A, et al. Applied Radiation and Isotopes, 2020, 165: 109295.
[3] Yi X, Walia E, Babyn P. Medical image analysis, 58: 101552 (2019).

Verification of newly developed dose calculation algorithm for BNCT by experiment using different shaped phantom

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[Introduction]

Clinical treatment using accelerator-based boron neutron capture therapy (BNCT) has been started. Accordingly, efficiency in the treatment planning becomes increasingly important. Monte Carlo (MC) method, which has been conventionally used as dose calculation algorithm for BNCT, has high calculation accuracy. However, it requires a long time for the calculation because of tracking particles until they completely stop. Therefore, we have been progressing development of the hybrid algorithm, that is a combination of MC and superposition methods, for the faster dose calculation. In this algorithm, moderation process of neutrons was calculated by MC method, and then thermalization process was modeled as a kernel. We experimentally verified the calculation accuracy of this algorithm in terms of thermal neutron flux, through comparison with the measured result using different-shaped phantoms.

[Materials and Methods]

Calculation using the hybrid algorithm was performed as follows; an isotropic kernel was derived by calculating thermal neutron flux distribution generated by a point source with the energy of 1 eV in sufficiently large geometry filled with water including boron. Also, the kernel was calculated by MC method using PHITS [1]. Next, in-phantom flux distribution of neutrons terminating by cut-off energy of 1 eV was calculated using PHITS. Finally, this distribution of neutrons that moderated to switching into the thermalization process was convolution-integrated with the kernel in the same way as a superposition method, and then thermal neutron flux distribution was derived. The calculated thermal neutron flux was compared with the measured value or the calculated value by the full-energy MC method using PHITS.

The thermal neutron flux distribution in water phantoms were experimentally determined by a gold activation method as follows; bare or cadmium covered gold wires were set on a central axis of neutron beam and in the off-axis direction in a cubic or cylindrical acrylic phantom filled with boric acid solution with boron-10 concentration of 23 ppm. Each phantom was irradiated by an epithermal neutron beam formed by LiF-containing polyethylene collimator with φ12 cm aperture at Kyoto University Reactor [2]. Subsequently, the gamma rays emitted from each of the gold wires with 0.5 or 1 cm length were measured by NaI(Tl) scintillation detector. The activation reaction rates were derived from the count rates, and then the thermal neutron flux distributions in each phantom were determined.

[Results and Discussion]

The thermal neutron flux distribution calculated by the hybrid algorithm was compared with the measured results for the verification of the algorithm. As a result of comparison, in both cases using two different shaped phantoms, the calculated results showed good agreement with the measured results at a distance ≥ 4 cm from the phantom surface on the central axis. While overestimating the measured results in the vicinity of the phantom

surface. Comparing it with the calculated result using the full-energy MC method, the similar trend was shown. The overestimation in the shallower region was considered to be due to the kernel modeling. The kernel was calculated in sufficiently large geometry filled with water, not considering leakage of neutrons from surface of the phantom in the experiment.

[Conclusion]

We experimentally verified the accuracy of the hybrid algorithm. The verification result confirmed that the thermal neutron flux calculated by the hybrid algorithm could partially reproduce the measured values using different shaped phantoms. We will progress the development aiming at improving the accuracy of this algorithm especially at the shallower depth and establish the algorithm comprehensively including the verification of calculation of fast neutron and gamma-ray doses.

Keywords:
BNCT, dose calculation algorithm, Monte Carlo, superposition

References:

[1] T. Sato, et al, Features of Particle and Heavy Ion Transport code System (PHITS) version 3.02, J. Nucl. Sci. Technol. 55, 684-690, 2018.
[2] Y. Sakurai, et al,The medical-irradiation characteristics for neutron capture therapy at the Heavy Water Neutron Irradiation Facility of Kyoto University Research Reactor, Med. Phys. 29, 2328-2337, 2000.

Study of gamma ray measurement in BNCT irradiation field by OSL technique

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For quality assurance and quality control of Boron Neutron Capture Therapy (BNCT), it is necessary to measure not only neutron flux (or fluence) but also gamma-ray dose in the irradiation beam.

Currently, quartz glass TLD (BeO) or twin ionization chamber technique are used for gamma-ray measurement in BNCT. However, the quartz glass TLD have been discontinued, and twin ionization chambers require gas flow, which is inconvenient for hospital operations. Therefore, we are evaluating a gamma ray detection method using the OSL (optically stimulated luminescence) technique in the BNCT irradiation field. The OSL detector consists of a BeO plate and a light-shielding case, and reads out the irradiation dose by light stimulation.

In this study, we compared OSL technique and quartz glass TLD using the accelerator BNCT system of Kyoto University. TLDs and OSLs were set at 20, 40, 60, and 120mm of the beam axis in the water phantom and were irradiated at 0.3C (= 300 sec).

As a result, the difference between the measured values of quartz glass TLD and OSL was within ± 5%. The OSL technique is a promising method for gamma-ray measurement in BNCT irradiation field, and we will consider it in detail in the future.

Keywords:
QA, TLD, OSL, gamma-ray

O66

Development of fast dose calculation algorithm for BNCT based on a combination of Monte Carlo and superposition methods

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[Introduction]

Boron neutron capture therapy (BNCT) using accelerator-based neutron source has been clinically started in 2020 under the Japanese national health insurance system. With increase in number of patients, efficiency in treatment planning process becomes more important. Monte Carlo (MC) algorithm, conventionally applied to BNCT dose calculation, has high accuracy, while requiring a long calculation time. Thus, the dose calculation using the MC algorithm can be a bottleneck in the treatment planning and lead to insufficient dose optimization. Aiming to reduce the calculation time, we have been developing a hybrid algorithm based on a combination of a neutron/photon transport calculation by the MC method and model-based kernel convolution. Outline of the hybrid algorithm is reported.

[Materials and Methods]

The Concept of the hybrid algorithm is based on separation of neutron transport physics into two phases, that is, moderation and thermalization. The moderation of neutrons, which can be treated as binary collisions and capture reactions mainly with hydrogen atoms, is calculated by MC method. Then, the thermalization of the moderated neutrons, which is complex process with collisions and thermal equilibrium mainly with molecular-bounded hydrogen atoms, is modeled as a kernel. The calculation of thermalization process, which is rather time consuming in particle tracking using MC method, can be reduced to a pre-calculated kernel to shorten the overall calculation time.

Calculation using the hybrid algorithm is performed as follows; the moderation process is calculated by using MC method, where the cut-off energy of neutron is set to around 1 eV as a switching energy from moderation to thermalization process, and then the flux distribution of neutrons terminating by the cut-off energy is convolution-integrated with the kernel modeling the thermalization. Various physical quantities related to the low energy neutrons, such as thermal neutron flux, boron dose, nitrogen dose, capture gamma-ray productions, can be prepared as a kernel. Other dose components: fast neutron and incident gamma-ray doses can be determined simultaneously in the MC simulation for the moderation process.

[Results and Discussion]

As an example, a calculation using a voxelized head phantom was performed to evaluate the accuracy and calculation time. The kernel for thermal neutron flux in an infinite volume of light water was modeled with the switching energy of 1 eV, by using PHITS[1]. The kernel was isotropic and prepared as a function of distance from the source, consisting of two parts; inversely proportional to square of distance and build-up due to thermalization. Comparison of the hybrid algorithm and conventional full-energy MC method was performed using the voxelized head phantom. In the both methods, PHITS[1] was used for MC transport calculation. In the calculations, an epi-thermal neutron beam at the KUR heavy water neutron irradiation facility[2] was used

as a neutron source, and the phantom was irradiated with the beam from the top of the head. Compared with results using the full-energy MC method, the calculation time was reduced to less than a half for running the same number of particles. The thermal neutron flux distribution showed good agreement in a deep region where the distance from the surface was greater than a few cm, while was overestimated in a shallower region. This overestimation was mainly due to insufficient consideration of reflection and leakage phenomena in a shallower region in the kernel modeling.

[Conclusion]

It was confirmed that calculation using the hybrid algorithm can shorten the calculation time, and is effectively working in a deep region, whereas improvement of the kernel modeling is needed especially in a shallower region. Overview of the hybrid algorithm and its effectiveness including the results for the other dose components will be reported.

Keywords

treatment planning, dose calculation algorithm, Monte Carlo method, superposition method

References:

[1] T. Sato, Y. Iwamoto, S. Hashimoto, T. Ogawa, T. Furuta, S. Abe, T. Kai, P. -E. Tsai, N. Matsuda, H. Iwase, H. Shigyo, L. Sihver, and K. Niita, Features of Particle and Heavy Ion Transport code System (PHITS) version 3.02, J. Nucl. Sci. Technol. 55, 684-690, 2018.

[2] Y. Sakurai, T. Kobayashi, The medical-irradiation characteristics for neutron capture therapy at the Heavy Water Neutron Irradiation Facility of Kyoto University Research Reactor, Med. Phys. 29, 2328-2337, 2000.

Development of the two steps ionization chamber for monitoring the neutron beam intensity

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In accelerator based BNCT, the electric current of charged particles irradiated to a neutron production target has been used for monitoring the neutron beam intensity. In this regard, the relationship between the electric current and thermal neutron flux in water phantom is confirmed as quality assurance (QA) before each treatment. It is desirable to measure neutron flux in real-time to confirm soundness of the target during the irradiation. In particular, it is important to measure fast neutron, which has higher biological effectiveness than epithermal neutron.

Currently, twin ionization chambers with graphite and tissue equivalent walls are attempted to separately measure gamma ray and neutron dose. However, the neutron dose includes not only fast neutron but thermal and epithermal neutron. In this study, we develop the ionization chamber capable of measuring fast neutron in high sensitivity and present the results of the simulation with PHITS.

The detector compromises a tissue equivalent plastic (A150) and two electrodes made of aluminum (Al). The chamber was enclosing tissue equivalent gas. The patterns of electrodes are A150-Al-Al and Al-A150-Al in order. When the middle of electrode is applied at voltage, the ionized charges generated in the sensitive areas of front and back gas region were collected with electrodes at both ends. Fast neutron events are able to be measured with the subtraction of gamma-ray events.

The detector was assumed to be a circular parallel plate type, and the simulation was performed by changing the diameter from 10 to 50 mm, the distance between the plates from 1 to 10 mm. The energy deposit distributions of charged particles generated in the gas regions were derived using PHITS. The amounts of ionized charges per irradiated neutron and gamma ray fluence were obtained by W-value of each charged particle. The validation of above simulation method was conducted with the comparison of the measurement results by twin ionization chambers.

As regards twin ionization chambers, the ratio of the amount of charge obtained by PHITS to experiment was 2.1, and we used it as a normalized factor. In the electrode pattern of A150-Al-Al, the contribution of fast neutrons was less than 50 %. On the other hand, in the electrode pattern of Al-A150-Al, the fast neutron contribution was improved up to 70 % by increasing the diameter to 50 mm. In each electrode pattern, the contribution of gamma ray was less than 1 %. It is confirmed that the detector was able to measure fast neutron in high sensitivity. However, this simulation was so simple model and didn't consider outer wall and Al thickness. In addition, the beam incident was assumed to be forward direction. However, in actual BNCT irradiation field, the beams are injected to the detector in several directions. Therefore, it is important to consider the detector model actually manufactured and the dependence on the incident direction.

In conclusion, we simulated the optimization of the ionization chamber sensitive to fast neutron in accelerator based BNCT irradiation field. The simulation of the ionization chamber with two steps parallel electrodes was

carried out. It was confirmed that taking into account only the radiations irradiated in the front, the detector was able to measure fast neutron in high sensitivity. In the future, we aim to the detector system that is less dependent on the incident direction.

Keywords:
fast neutron, ionization chamber, neutron monitor

O72

A study on 2D component-discrimination estimation for BNCT irradiation field using a PVA-GTA-I radiochromic gel dosimeter

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INTRODUCTION: Irradiation field for BNCT is the mixed field of thermal neutrons, epi-thermal neutrons, fast neutrons, and gamma rays, so the discrimination estimation is necessary for each dose component in the irradiation field characterization. The point-wise estimation using activation foil, thermo-luminescent dosimeter (TLD), ionization chamber, etc., is mainly performed at present, but two-dimensional (2D) estimation is also needed. As part of the advancement in characterization for BNCT irradiation field, a study was performed for the 2D component-discrimination estimation using a radiochromic gel dosimeter base on polyvinyl alcohol - glutaraldehyde – iodide (PVA-GTA-I) [1].

MATERIALS AND METHODS: Three-layered planer gel dosimeter was prepared, as shown in Figure 1. Each planar gel dosimeter was 10 cm in width, 10 cm in length and 0.3 cm in thickness. The first layer (Gel-1) was a PVA-GTA-I gel dosimeter containing boric acid ($B(OH)_3$) of natural abundance for boron-10 or lithium sulphate (Li_2SO_4) of enrichment for lithium-6 as the sensitizers for thermal neutrons. The second layer (Gel-2) was a normal PVA-GTA-I gel dosimeter without the sensitizers. The third layer (Gel-3) was a PVA-GTA-I gel dosimeter consisting of heavy water instead of light water. For fast neutrons, the recoiled protons or deuterons due to the elastic scatter of hydrogen or deuterium mainly contribute to dose. For thermal neutrons, the nuclear reactions of boron-10 or lithium-6 mainly contribute to dose.

The response characteristic for gamma rays was estimated using Co-60 Gamma-ray Irradiation Facility. The response characteristic for neutrons was estimated by the irradiation experiments using three irradiation modes for thermal, epi-thermal and mixed neutrons at Heavy Water Neutron Irradiation Facility (HWNIF) of KUR [2], and by the simulation calculation using Particle and Heavy Ion Transport-code-System (PHITS) [3].

The verification experiment for 2D component-discrimination estimation was performed using the mixed neutron irradiation mode of KUR-HWNIF. The size of the collimator aperture was 12 cm in diameter, and the three-layered planer gel dosimeter was placed at the collimator exit to hang on the aperture edge.

The irradiated gel dosimeters were scanned using a scanner and the transmission images were obtained. The transmission images were analyzed using a Python pro-gram, the net optical density (net OD) was calculated from the analogue digital conversion (ADC) values, and the response characteristic was estimated.

RESULTS AND DISCUSSION: From the response characteristic experiment for gamma rays, the high linearity was confirmed between the response and dose from 0 to 20 Gy. From the response characteristic experiment for neutrons, the response curve to dose-weighted linear energy transfer (LET) was obtained. Using this response curve, the correction factors regarding LET-dependency for the recoiled protons, recoiled deuterons and the thermal neutron reactions with boron-10 and lithium-6, were obtained.

From the verification experiment for 2D component-discrimination estimation, the 2D dose distributions were obtained. It was confirmed that the 2D distribution for thermal neutrons were relatively in close agreement with the estimated result by activation method using gold thin film. The absolute value by the gel dosimeter was almost two times larger compared with the activation method. It is thought that the components scattered in the gel dosimeter contributed additionally. For gamma rays, the 2D dose distribution was in good agreement with the estimated result by TLD.

CONCLUSION: The feasibility for the 2D component-discrimination estimation using the three-layered planer gel dosimeter was confirmed. In future, the sensitivity improvement and thickness reduction of this gel dosimeter will be studied. Also, the dependency for LET will be precisely estimated.

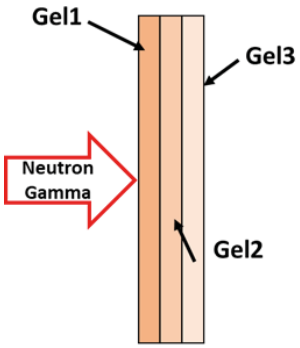

Figure 1. *Schematic of three-layered planer gel dosimeter.*

Keywords:
radiochromic gel dosimeter, PVA-GTA-I, component discrimination, 2D estimation, LET-dependency

References:

[1] S. Hayashi et al., J. Phys.: Conf. Ser. (accepted) (2021).
[2] Y. Sakurai and T. Kobayashi, Nucl. Instr. Meth. A 453 (2000) 569-596.
[3] T. Sato et al., J. Nucl. Sci. Technol. 50 (2011) 913-923.

Mimac-FastN, a mobile and directional fast Neutron spectrometer and an active phantom for BNCT

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Non-pulsed neutron field spectroscopy of epithermal and higher energies is challenging for the presently available detector technologies. Mimac-FastN is a micro-TPC (Time Projection Chamber) based on a micro-pattern detector coupled to fast self-triggered electronics. The chamber is filled with a gas that constitutes the converter of fast neutrons into nuclear recoils able to ionize the gas in the active volume [1].

The measurement of the neutron capture rate on a foil comprising a known amount of ^{10}B nuclei is an additional feature to characterize the thermal and the epithermal components of the neutron field. This can be done using a $^{nat}B_4C$ layer comprising 20 % of ^{10}B, put it on the cathode of the detector. The boron coating consists of an IBS (Ion Beam Sputtering) deposit of 500 nm thick on an aluminum sheet. The alpha and ^{7}Li particles resulting from neutron captures on the ^{10}B nuclei, release their energy in ionization in the gas mixture, and through 3D reconstruction, their tracks associated to the energy released in ionization are recorded

The energies deposited in ionization by the ^{4}He and ^{7}Li particles are measured on the Flash-ADC, and their tracks are imaged on the pixelated anode. The ability to detect these particles resulting from neutron capture on ^{10}B and to measure their energy released in ionization has already been demonstrated with a gas mixture that consists of ^{4}He and 5% of CO_2 at 700 mbar, for energy calibration purpose [1]. A selection of all the tracks whose interaction points are located on the boron coating projection leads to the energy spectrum shown in Fig. 1. This measurement opens the possibility to use the detector as an active phantom for BNCT placed in a high flux epithermal neutron field just after the moderator and counting the neutron captures produced at the coating level simulating the tumor and the amount of ^{10}B placed on it by a previous vectorization. In this way a boron dose measurement can be performed with a controlled amount of boron in the epithermal neutron field. Measurements will be presented for the first time.

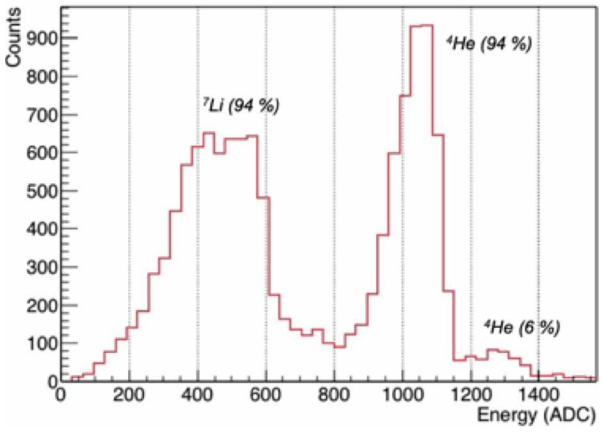

Figure 1. : Measured ionization energy spectrum of the 4He and ^{7}Li particles resulting from neutron capture on the boron coating, in a neutron beam of 3 MeV moderated through 5 cm of HDPE. This spectrum is the raw data from the Flash-ADC.

Keywords:
Neutron spectrometry, active phantom

References:

[1] N.Sauzet et al., "*Fast neutron spectroscopy from 1 MeV up to 15 MeV with Mimac-FastN, a mobile and directional fast neutron spectrometer*", NIM.A, vol. 965, 2020.

O85

Study on the optimization methods of thermal neutron flux distribution by overlapping multiple irradiation fields for superficial tumors in accelerator-based BNCT

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We have confirmed that it can form uniform thermal neutron distribution using a bolus in accelerator-based BNCT. In the case of superficial tumor like melanoma, it was found that the small irradiation field could be uniform thermal neutrons in the plantar position. However, it is difficult to form a uniform thermal neutron distribution with a single irradiation using a bolus for relatively shallow and widely spreading tumors such as angiosarcoma and malignant meningioma.

In this study, we create irradiation fields that form various thermal neutron distributions by installing neutron moderators in a collimator aperture. The method that can uniform thermal neutron irradiation by combining several of these fields was proposed.

SERA was used to evaluate the thermal neutron flux. Appropriate CT images were selected from the public patient image data of the Cancer Imaging Archive, and 3D data was created using 3D-CAD software. A head phantom was created using a 3D printer. A CT images of the head phantom was obtained to compare with experimental results.

The cyclotron-based epithermal neutron source at the Institute for Integrated Radiation and Nuclear Science, Kyoto University was used as the neutron source. The collimator diameter was 18 cm. Polyethylene and LiF were selected as neutron moderators. The irradiation was assumed to be top of the head. The thermal neutron flux at the evaluation point was calculated.

The number of combinations was set to a maximum of three, because the current neutron source intensity does not allow for only two or three times in one irradiation condition. We investigated whether it is possible to irradiate thermal neutrons uniformly by combining several irradiation fields. The uniformity index u is defined as follows when the thermal neutron flux is defined as Φ_i and the mean value of the thermal neutron flux is defined a Φ_{av}:

$$u = \sum_{i=1}^{n} \left| 100 \times \left(1 - \frac{\Phi_i}{\Phi_{av}} \right) \right| / n$$

Irradiation field - (IF-) A was set to a polyethylene disk with a radius of 9 cm and a thickness of 2 cm as a neutron moderator. The thermal neutron distribution is high in the center and low at the edges of the irradiation field. IF-B was a neutron moderator with a combination of polyethylene and LiF. LiF was set at the center of the irradiation field to increase the neutron intensity at the edge relatively. The uniformity indexes in 120 mm in diameter of IF-A and IF-B were 24.8 and 15.3, respectively. When irradiation was performed by combining

the irradiation time ratio of irradiation fields A and B as 1:5, the uniformity was improved to 6.1. The average thermal neutron flux in the region was 4.0×10^8 n/cm^2/s.

As a result, it was revealed that a uniform thermal neutron distribution could be formed for a wide range of irradiated areas by combining multiple irradiation fields. We confirmed that accelerator based BNCT can be applied to relatively wide superficial tumors.

In the future, we plan to evaluate a uniform thermal neutron flux distribution in superficial region with given thickness to assume angiosarcoma and malignant meningioma. We will also conduct irradiation tests by actual measurements.

Keywords:
superficial tumors, overlap, 3D printed phantom, multi-field irradiation

References:

[1] Grossberg A, et al., M.D. Anderson Cancer Center Head and Neck Quantitative Imaging Working Group. (2020) HNSCC [Dataset]. The Cancer Imaging Archive.
[2] Grossberg A, et al., (2018) Imaging and Clinical Data Archive for Head and Neck Squamous Cell Carcinoma Patients Treated with Radiotherapy. *Scientific Data* 5 :180173 (2018)
[3] Elhalawani, H., *et al.* Matched computed tomography segmentation and demographic data for oropharyngeal cancer radiomics challenges. *Sci Data* 4, 170077 (2017).
[4] Clark K, et al., The Cancer Imaging Archive (TCIA): Maintaining and Operating a Public Information Repository, Journal of Digital Imaging, Volume 26, Number 6, December, 2013, pp 1045-1057.

Development of Deterministic Dose Evaluation Algorithm for Neutron Capture Therapy Using Convolution/Superposition Method

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Introduction

Monte Carlo techniques are the most favored tool for BNCT dose evaluation due to their accuracy in radiation dosimetry and applicability to various treatment conditions. Nevertheless, the Monte Carlo method is not the first choice for photon radiotherapy as it is still time-consuming and requires significant computational power. The convolution/superposition algorithm is widely used in conventional radiotherapy as it provides dose calculation results within a few minutes with reasonable accuracy, making it suitable for the clinical environment[1]. The convolution/superposition dose calculation method utilizes two distributions of physical quantity; the total energy released per unit mass (TERMA) and the energy deposition kernel. TERMA calculation models the primary photons that interact with the material. The kernels represent the energy transport and dose deposition of secondary particles caused by point irradiation. The released energy dissemination and deposition through the media are predicted by convoluting TERMA with the kernel. In this work, we applied the convolution/superposition technique to the neutron dose evaluation for a clinically practical BNCT treatment planning system.

Materials and Methods

To supplant photon TERMA in neutron convolution/superposition, we suggest an original concept of total energy generated per unit mass (TEGMA) by nuclear interaction. For a specific nuclear interaction, TEGMA is defined as the product of mean energy released or generated per each interaction and the reaction rate per unit mass. Three TEGMA libraries were constructed corresponding to the three main nuclear reactions that contribute to neutron dose in BNCT,, , and . In reaction, the Q-values are 2.33 MeV and 2.81 MeV accounts for 94% and 6% respectively. As for reaction, the Q-value is 0.626 MeV. The cross-sections of each element and energy were manually calculated by linear interpolation of microscopic cross-section data from ENDF/B-VII.1 library[2] and atomic number density of brain from ICRU report 46[3]. For interaction, the hydrogen kerma factor[4] was adopted for hydrogen. The neutron flux in the medium by irradiation was simulated by MCNP 6.2[5] code. The calculated dose results from convolution/superposition have been compared with PHITS 3.02[6] Monte Carlo simulation code in virtual homogeneous phantom with various irradiation beam field sizes.

Results

PHITS result uncertainty was less than 3% at a depth of 2 cm. The discrepancies or relative error, measured at a depth of maximum dose, were within 5% and got smaller as the beam field size increases. The comparison results of the time taken for dose calculation between convolution/superposition and PHITS were shown in Table 1.

	CPU(Intel)		Calculation time	Uncertainty at a depth of 2cm
	Cores	Processor base frequency		
CS	1	2.80 GHz	56 sec	—
PHITS	4	2.80 GHz	48 h	3~5%
	48	2.67 GHz	4 h	

Table 1. *Dose calculation time comparison between C/S neutron dose calculator and PHITS Monte Carlo code for 3030 mono-directional neutron beam in a virtual homogeneous phantom*

Keywords:
dose calculation, convolution/superposition, Monte Carlo simulation

References:

[1] R. Mohan, C. Chui, and L. Lidofsky, Differential pencil beam dose computation model for photons, Medical Physics, Volume 13, Issue 1, pp. 64-73, 1986
[2] B. Chadwick *et al*., ENDF/B-VII.1 Nuclear Data for Science and Technology: Cross Sections, Covariances, Fission Product Yields and Decay Data, Nuclear Data Sheets, Volume 112, Issue 12, 2011
[3] R. White, *et al*., Report 46, Journal of the International Commission on Radiation Units and Measurements, Volume os24, Issue 1, 1992
[4] R. S. Caswell, J. J. Coyne, and M. L. Randolph, Kerma Factors for Neutron Energies below 30 MeV. Radiation Research, Volume 83, Issue 2, pp. 217–254, 1980
[5] Werner *et al*., MCNP Version 6.2 Release Notes, United States, 2018
[6] T. Sato *et al*., Features of Particle and Heavy Ion Transport code System (PHITS) version 3.02, Journal of Nuclear Science and Technology, Volume 55, Issue 6, pp. 684-690, 2018

O98

Development of Bayesian Predictive Platform for Blood Boron-10 Pharmacokinetics following Intravenous Infusion of [10B]L-4-BORONOPHENYLALANINE

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Boron neutron capture therapy (BNCT) allows high-precision radiotherapy against tumor using boron-10 (^{10}B) with tumor-localizing characteristics and strong tendency to capture thermal neutrons. It is important to accurately predict the blood ^{10}B concentration during the neutron irradiation to deliver the prescribed dose as planned. Compared to the neutron amount (flux, n/cm^2/s) which can be measured or controlled with precision, blood ^{10}B concentration may not be easily predicted due to inter- and intra-subject variability after infusion in each individual. The purpose of the study is to develop user-friendly and versatile Bayesian predictive platform for pharmacokinetics (PK) of ^{10}B which is clinically applicable in BNCT.

The predictive platform is based on NONMEM® 7.4 (ICON Development Solutions, USA), and R (version 4.03) with Shiny package. NONMEM stands for nonlinear mixed effect modeling, and it is nonlinear regression software solving PK and pharmacodynamic problems taking both fixed and random effect (between subject and within subject variabilities) into account. Population PK model for ^{10}B was constructed using blood ^{10}B concentration over time data following intravenous infusion of boronophenylalanine (BPA) which were digitized from previous study results[1-7]. The population PK model is used as prior distribution model for Bayesian prediction, which is performed by mode a posteriori (MAP) estimation using maxeval=0 in NONMEM. Individual blood ^{10}B concentration data in NONMEM format is generated via user-friendly interface using Shiny package in R. Bayesian prediction and analysis of the result is conducted by running R script.

The predictive platform worked stable and predicted the individual blood ^{10}B concentration with high accuracy and reliability. This platform will not only improve the uncertainties in blood ^{10}B concentration prediction but also deliver the prescribed dose with high accuracy.

Keywords:
predictive platform, Bayesian, boron neutron capture therapy, individualization

References:

[1] ´WS Kiger, MR Palmer, K J Riley, R G Zamenhof, P M Busse. Pharamacokinetic modeling for boronophenylalanine-fructose mediated neutron capture therapy: 10B concentration predictions and dosimetric consequences. Clinical Trial J Neurooncol. 2003;62(1-2):171-86.
[2] WS Kiger; MR Palmer, KJ Riley, RG Zamenhof, PM Busse. A Pharmacokinetic Model for the Concentration of 10B in Blood after Boronophenylalanine-Fructose Administration in Humans. Radiat Res. 2001;155 (4): 611–618.

[3] PM Ryynänen, M Kortesniemi, JA Coderre, AZ Diaz, P Hiismäki, SE Savolainen. Models for estimation of the (10)B concentration after BPA-fructose complex infusion in patients during epithermal neutron irradiation in BNCT. Int J Radiat Oncol Biol Phys. 2000;1;48(4):1145-54.

[4] Zhong Yong, Zewen Song, Yongmao Zhou, Tong Liu, Zizhu Zhang, Yanzhong Zhao, Yang Chen, Congjun Jin, Xiang Chen, Jianyun Lu, Rui Han, Pengzhou Li, Xulong Sun, Guohui Wang, Guangqing Shi, Shaihong Zhu. Boron neutron capture therapy for malignant melanoma: first clinical case report in China. Chin J Cancer Res. 2016 Dec;28(6):634-640.

[5] H Koivunoro, E Hippeläinen, I Auterinen, L Kankaanranta, M Kulvik, J Laakso, T Seppälä, S Savolainen, H Joensuu. Biokinetic analysis of tissue boron (^{10}B) concentrations of glioma patients treated with BNCT in Finland. Appl Radiat Isot. 2015;106:189-94.

[6] Andrea Wittig, Laurence Collette, Klaas Appelman, Sandra Bührmann, Martin C Jäckel, Karl-Heinz Jöckel, Kurt Werner Schmid, Uta Ortmann, Raymond Moss, Wolfgang A G Sauerwein. EORTC trial 11001: distribution of two 10B-compounds in patients with squamous cell carcinoma of head and neck, a translational research/phase 1 trial. Clinical Trial J Cell Mol Med. 2009;13(8B):1653-1665.

[5] H Fukuda, J Hiratsuka, C Honda, T Kobayashi, K Yoshino, H Karashima, J Takahashi, Y Abe, K Kanda, M Ichihashi, et al. Boron neutron capture therapy of malignant melanoma using 10B-paraboronophenylalanine with special reference to evaluation of radiation dose and damage to the normal skin. Clinical Trial Radiat Res. 1994;138(3):435-42.

O112

Estimation of the efficacy of boron neutron capture therapy for the head-and-neck cancer by using tumor control probability model

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The tumor control probability (TCP) model has been used for estimating the response of the radiation therapy since 1980. More models were developed when more clinical data were collected. In Taiwan, unlike photon therapy, boron neutron capture therapy (BNCT) is still at the stage of the clinical trials without standard prescription dose. The tumor response and dose distribution from protocol I of the clinical trial of the recurrent head-and-neck (H&N) cancer conducted by Taipei Veterans General Hospital and National Tsing Hua University were used to verify the TCP model established in this study. The results showed that under the condition of using the Universal Survival Curve (USC) model as a biological model of dose conversion, the TCP calculated by the Equivalent Uniform Dose (EUD) based TCP model can be used to well correlate the relationship between the tumor response and dose distribution of the patients of recurrent H&N cancer. In addition, after using the analysis of the Receiver Operating Characteristic curve, 20% and 50% of TCP indicated the partial response and complete response of H&N cancer, respectively. This study also indicated that when BNCT was used to treat recurrent H&N cancer, the minimum dose was an important factor on the efficacy of the treatment. The 18 Gy-w of the minimum dose presented at least 60% of TCP.

Keywords:
tumor control probability, head-and-neck cancer

Diagnostic, infusion and blood boron measurement strategies to reduce calculated BNCT dosimetry uncertainties based on multi-compartment pharmacokinetic models

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Dosimetry for boron neutron capture therapy (BNCT) depends fundamentally on the spatial distributions of boron-10 in the tumor and surrounding tissues. These distributions (and their relative weight to each other) change continuously during and after infusion of the boron pharmaceutical, making the dose distribution from boron reaction products strongly dependent on the start time of each neutron beam relative to the time-dependent infusion rate. The temporal relationship between the boron infusion schema and tissue concentration varies between patients, and with in-vivo boron measurements not currently available, pharmacokinetic models provide an alternative to using the same tumor-to-blood and tissue-to-blood boron ratios for all patients at all time points.

Previous authors have developed 2-compartment models for the time-dependent blood boron concentration as a function of the time-dependent boronophenylalanine (BPA) infusion, demonstrating the accuracy of the model with blood boron measurements in BNCT patients [1]. In addition, authors have used ^{18}F-BPA (fructose-complexed) PET scans, verified with boron concentrations measured from tissue biopsies, in 3-compartment models to predict the time-dependent boron concentrations in various tissue types as a function of time-dependent blood (plasma) concentration [2]. The accuracy of each model is significant when the patient-specific model parameters are known, but in clinical practice many blood draws and PET scans would be required to complete both models. Using average parameters will result in uncertainties in boron concentrations and dosimetry calculations.

Future BNCT treatments based on new therapeutic boron pharmaceuticals and PET tracers cannot assume the same kinetics as BPA and ^{18}F-BPA. This suggests the need for a general strategy to improve dosimetry uncertainties by adjustment of: PET diagnostics; treatment planning parameters; time-dependent boron infusion profiles; and timing and quantity of blood boron measurements. The basis of this approach is combining the 2-compartment infusion/blood model with the 3-component blood/tissue models, which will be demonstrated using published clinical data for BPA and ^{18}F-BPA in glioblastoma multiforme. While this approach gives guidance to achieving similar dosimetric behavior for different drug/tracer combinations, these models have key limitations, including an inability to model uptake heterogeneities within the tumor and tissue compartments, as well as uptake limits due to blood brain barrier (BBB) or tissue necrosis, which will be discussed.

Keywords:
pharmacokinetics, compartment model, BPA, F-BPA, BNCT dosimetry

References:

[1] Kiger et al, Journal of Neuro-Oncology 62: 171-186 (2003).
[2] Imahori et al, Clinical Cancer Research 4: 1833-1841 (1998).

O120

Development of a novel compact isotropic Neutron spectrometer for BNCT

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In recent years, due to the introduction of accelerator-based BNCT facilities, the interest of the medical and scientific communities for BNCT dramatically increased.

Monitoring and characterization of neutron beams for intercomparison of different facility sites and accelerator types are becoming mandatory [1] This stimulates the development of dedicated dosimetry and spectrometry techniques.

This work aims to develop a novel compact spectrometer with an isotropic response, suitable for in-phantom irradiation, highly sensitive in the energy interval ranging from thermal to 100 keV,

The idea is a spherical device organized on concentric shells of different materials exhibiting neutron radiative capture resonances at different energies, so that every material will be sensitive in a specific energy domain. Moderating shells of polyethylene will be added to better resolve different energy components and to extend the sensitivity range. The spherical geometry will guarantee to have an isotropic response and to consider the neutron backscattering components that play a crucial role in BNCT.

The novelty of this idea is the combination of the Neutron Activation Analysis (NAA) together with the moderation spectrometers techniques.

Extensive simulations using the MCNP code of this new device, for the choice of the suitable materials and geometries have been done

Materials as In, Au, As, Pr, Mn, Cu, Na, Cl, V, Ti have been considererd as they offer high radiative capture cross-sections in different energy intervals, their γ emissions have measurable energies and reasonable half-lives.

The data analysis requires a detailed study of the overall γ spectrum taking in to account the specific material activation spectra shapes.

The energy distribution of the neutron fluence is the result of an unfolding procedure that uses the activation data from the different shells.

A multi-material compact spectrometer for in-phantom measurement will be a novelty for the BNCT applications, but It also could be of great interest for any application of spectrometry and dosimetry such as also criticality accident dosimetry or aerospatial neutron dosimetry.

Keywords:
Neutron spectrometry, BNCT, activation foils, in-phantom dosimetry.

References:

[1] IAEA. *"Advances in Boron Neutron Capture Therapy"*. Ref. No: F1-TM-1905174 EVT 1905174 (2020).

O121

Detailed dosimetry calculation for in-vitro experiments and its impact on clinical BNCT.

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Boron Neutron Capture Therapy (BNCT) is a form of hadrontherapy based on the interaction between low energy neutrons and ^{10}B atoms. The neutron capture reaction in boron releases two high-LET, short range particles which cause non-reparable biological damage. The total absorbed dose administered to tissues is due to a mixed field of radiations that have different biological effectiveness. As the relationship between the absorbed dose and the induced biological effects is not unique, the translation of BNCT doses into a photon reference radiation dose is necessary. Thus, dose calculation models based on reliable radiobiological data are required to predict and understand the clinical outcome.

In this work, computational dosimetric studies for the irradiation of monolayer tumour cultured cells with photons and BNCT are presented. Strategies for Monte Carlo calculations, including both simplified uncharged particles and detailed secondary charged particles transport, are shown and discussed for the irradiation set-ups used in two BNCT projects. The dose-response curves reported for the rat osteosarcoma UMR-106 and human metastatic melanoma Mel-J cell lines were modified according to the correction factors determined from the computational studies and irradiation protocol. New radiobiological parameters of the photon iso-effective dose models for osteosarcoma and metastatic melanoma were obtained and dosimetry implications in a clinical setting were assessed.

Results showed that, if charged particle equilibrium is assumed for the calculation of doses in the monolayer-cultured cells, the KERMA values overestimate absorbed doses of all radiation components of interest in BNCT (12%, 40% and 18% for boron, neutron and gamma components in the case of osteosarcoma, and 8%, 36% and 6%, respectively, for melanoma experiments).

Detailed calculations for the osteosarcoma irradiation significantly impact on the relative biological effectiveness factor for the neutron component $RBE_{1\%}$, increasing the factor by more than 30% ((1.5 ± 0.2) vs (2.2 ± 0.4) for KERMA and absorbed dose, respectively). The fact that the mean $RBE_{1\%}$ value sensibly

changed highlights the importance of performing detailed dose calculations for *in-vitro* experiments. Since the contribution of the neutron dose is of importance particularly for the dose-limiting normal tissues, an increment of more than 30% in the biological effectiveness may lead to a different treatment prescription or to a more adequate analysis of the relationship between dose and radiotoxic effects.

In terms of dosimetry implications on the clinical BNCT, the assessment of cutaneous melanoma patients treated in Argentina shows that the use of KERMA approximation for cell survival curves leads to an underestimation of the delivered doses. Since this impacts on the capability of predicting the control of the lesions, the proposed dose calculation methods for *in-vitro* experiments are highly relevant for the clinical BNCT.

Keywords:
Boron Neutron Capture Therapy, computational dosimetry, CPE, in-vitro experiments, photon isoeffective dose, TCP.

O123

Comparison of photon isoeffective dose models based on *in-vitro* and in *in-vivo* radiobiological data for head and neck cancer

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Introduction

Comparison of BNCT with photon radiation therapies requires a dose calculation model that allows to estimate adequate photon-equivalent values. With a photon isoeffective dose, medical doctors can prescribe doses and predict the outcome of the therapy according to the clinical experience gained with photon radiotherapy. In this work, we address the question of whether or not the nature of the experimental data used to derive the parameters of the isoeffective photon model, i.e., in-vitro versus in-vivo radiobiological data, affects the dosimetry results and the treatment predictions for head and neck (HN) cancer.

Materials and methods

The primary human cell line UT-SCC-16A was used to determine the survival fraction as a function of dose. Photon and neutron irradiations of monolayer-cultured cells were performed using a 6 MV Linac accelerator (Turku University Hospital, Finland) and a thermal column of a TRIGA reactor (University of Pavia, Italy), respectively. The radiobiological (RB) parameters of the photon and BNCT survival models, obtained by non-linear minimization methods, were used to construct the photon isoeffective dose model based on in-vitro data. RBE and CBE factors for 1% cell survival level were also determined and compared to the values used in the clinical BNCT of HN cancer.

Thirteen BNCT treatments carried out in Finland for squamous cell carcinoma (SCC) patients were recreated with MCNP, using Multicell-based anatomy reconstructions and the irradiation conditions of each patient. Absorbed dose distributions in tumour for the different components of interest in BNCT were determined from simulations. The photon isoeffective dose model based on in-vitro data was implemented in BNCTAr: dosimetry Tool. Tumour doses were obtained and compared to those obtained with the model based on in-vivo data [1].

The clinical impact of considering the different dose models was assessed computing tumour control probabilities (TCP). For this, a suitable TCP model derived from hypofractionated photon radiotherapy data for SCC patients [2] and inhomogeneous doses was constructed. Conclusions based on both doses and control probabilities are presented

Results

The RB parameters of the survival models show that the alpha/beta ratio for the gamma component is greater than 100 Gy, and that beta values for the high-LET components are zero. This evidences that the cell killing for the UT-SCC-16A human line is mainly due to single radiation tracks that produce lethal lesions with a yield proportional to the dose.

$RBE_{1\%}$ and $CBE_{1\%}$ factors derived from in-vitro experiments are (4.2±1.1) and (4.4±0.7), values 30% and 15% higher than those used in the clinical BNCT of HN cancer.

The dosimetry of the 13 SCC patients shows that regardless of the nature of the RB parameters, photon isoeffective doses are much lower than the corresponding RBE-weighted tumour values. Tumour doses obtained with the in-vitro and in-vivo data-based models show average differences of 10%, 17% and 24% for the minimum, mean and maximum values. The most likely values of controlled tumours based on TCP calculations are (9.1±0.3) for RBE-weighted doses, and (7.6±0.4) and (8.0±0.4) for in-vitro and in-vivo data-based isoeffective doses, respectively. Statistical analyses considering that 6/13 lesions were controlled show that the difference between the predicted and observed number of controlled tumours for RBE-weighted doses is very unlikely (p-value=0.036). Thus, the model is not able to explained the clinical results (i.e., is rejected). On the contrary, both isoeffective dose models predict a number of controlled tumors statistically compatible with clinical outcome (p-values>0.2).

Conclusion

Photon isoeffective dose models based on in-vitro and in in-vivo radiobiological data can explain the total number of controlled tumour observed in HN cancer treatments with BNCT.

Keywords:
photon isoeffective dose, *in-vivo* oral cancer model, *in-vitro* cell survival, TCP

References:

1. González et al., Phys Med Biol 62, 7938-7958 (2017).
2. Rwigema et al., Am J Clin Oncol. 34(4): 372–379 (2011).

O124

Evaluation of the macroscopic and microscopic approaches for calculating photon isoeffective doses in Boron Neutron Capture Therapy

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Boron Neutron Capture Therapy is characterized by the interaction of a mixed radiation field with biological tissues. The main secondary charged particles that contribute to the total absorbed dose are alpha particles, lithium ions, protons and electrons. These products generate ionization patterns in living cells that may result in different cellular injury for the same absorbed dose. The fact that there is not a unique relationship between absorbed dose and induced biological effects, prompts the need for translation of BNCT doses into a reference radiation dose capable of predicting clinical outcomes.

This work presents the first study carried out to evaluate and compare two approaches introduced in BNCT for the estimation of the photon isoeffective dose. These approaches, referred to as macroscopic and microscopic photon iso-effective dose models, have the following characteristics. The macroscopic formalism assumes that calculations are independent of the spatial scale. This formalism takes into account synergism between different radiations and sublethal damage repair, incorporating mixed terms and the Lea-Catcheside factor into the probability models describing biological effects [1-2]. In contrast to this approach, the microscopic model deals with absorbed doses on cellular and sub-cellular scales. Based on the stochastic microdosimetric kinetic model, this approach can incorporate information on the intracellular and intercellular boron distributions [3].

In this work, we constructed the macroscopic photon isoeffective dose model based on the *in-vivo – in-vitro* cell survival data using squamous cell carcinoma (SCC) VII tumor-bearing C3H/He mice [4]. The radiobiological parameters of the model were obtained by fitting the photon and BNCT survival expressions to the experimental data. For this, a simultaneous non-linear minimization involving BNCT beam only and (BNCT + boron compound) was performed.

The obtained macroscopic model and the corresponding microscopic approach were used to compute depth-dose profiles along the central axis of a water-filled cylindrical phantom irradiated with the Tsukuba accelerator-based neutron beam iBNCT [5]. Doses were normalized to achieve a (neutron+gamma) absorbed dose of 5 Gy at the entrance of the phantom considering ^{10}B concentration values of 10 ppm and 40 ppm. Relative differences between estimations were computed and obtained results were analyzed considering corresponding absorbed dose values.

Cell surviving fractions (SF) using the radiobiological parameters obtained with the two approaches were calculated at 2 cm depth inside the cylindrical phantom. For SF calculations using the macroscopic approach, two different conditions regarding sublethal damage repair were evaluated. For SF calculations using the microscopic approach, both homogeneous and heterogeneous distributions of ^{10}B atoms at cellular level were considered. The relative dose components for the *in-vivo – in-vitro* SF experiment were similar to those obtained for the case of 40 ppm at 2 cm depth in the cylindrical phantom. Then, the correctness of predicted cell survival curves was discussed in the light of to the reported experimental data.

Photon iso-effective doses obtained in the cylindrical phantom with the two models based on the *in-vivo – in-vitro* cell survival data using SCC VII tumor-bearing C3H/He mice were compared to calculations carried out with the macroscopic model based on RB parameters from the *in-vivo* oral cancer model in the hamster cheek pouch [2].

Finally, ongoing calculations of photon iso-effective doses using a realistic irradiation scenario with a voxel phantom and patient data will pave the way to evaluate the relevance of the comparison in the clinics of BNCT.

Keywords

photon isoeffective dose, stochastic microdosimetric kinetic model, carcinoma cell survival assay

References:

1. González & Santa Cruz., Rad Res 178, 609-621 (2012).
2. González et al., Phys Med Biol 62, 7938-7958 (2017).
3. Sato et al., Sci Rep 8, 988 (2018).
4. Masunaga et al., Springer Plus 3:128 (2014).
5. Kumada et al., Appl Radiat Isot 88:211-215 (2014).

O140

Development of a single moderator neutron spectrometer for routine monitoring of therapeutic neutron beams

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A single moderator neutron spectrometer with directional response and emphasized resolving power in the epithermal domain was conceived and prototyped within the INFN project ENTER_BNCT. The device, called NCT-WES (Neutron Capture Therapy - Wide Energy Spectrometer), condenses the functionality of a Bonner Sphere spectrometer in a cylinder embedding six thermal neutron detectors in previously optimized positions. NCT-WES is a polyethylene cylinder with 36 cm diameter and 41.5 cm height. To achieve a sharply directional response, the sensitive part is shielded with a thick barrier made of polyethylene and borated rubber, except in the direction identified by the collimating aperture. Semiconductor-based thermal neutron detectors are used as internal thermal neutron detectors. The design, performed with MCNP6, was oriented to emphasize the spectrometric capability in the epithermal range and to achieve a limited weight (about 40 kg).

This communication describes NCT-WES, its response matrix, the experimental tests conducted to verify its response matrix, and comments possible applications in neutron capture therapy.

Keywords:
single moderator neutron spectrometer, neutron spectrometry, unfolding

Exploring MANTA-Ray: A Treatment Planning System especially developed for BNCT

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A treatment planning system (TPS) plays a major role for a successful radiotherapy, directly influencing the calculated dose accuracy, and thus the treatment quality. Multifunctional Arithmetic for Neutron Transportation Analysis (MANTA-Ray), a TPS especially designed for BNCT, which aims to provide high precision dose calculation with maximizing the efficacy. The accuracy of estimated doses, medical image processing, and irradiation setting flexibility are the three top-priority considerations in developing MANTA-Ray, while other factors like user-friendly interface, fluent working flow among different functional units in BNCT, and calculation speed are also taken into considerations. Some novel features are given as follows.

1. HU-based conversion and embedded tissue material library

Dose calculation accuracy highly depends on the material composition, which affects the neutron transportation and reactions with elements in the voxels, especially with the hydrogen atoms. A well calibrated ICRU material library is embedded in MANTA-Ray, which can be derived from a conversion curve using the HU numbers in CT images. This new feature significantly improves the accuracy in voxel model construction and the attributed dose estimation.

2. COMPASS Monte Carlo dose engine

COMPASS (COMpact PArticle Simulation System) is a dedicated Monte Carlo code (dose engine) for BNCT, which is seamlessly integrated in MANTA-Ray. Optimized cross-section library, parallel computing, and various variance reduction techniques are applied to speed up the particle transportations. A benchmark was performed between COMPASS and MCNP6, and results agreed well with no significant statistical difference; however, COMPASS needs only half of the calculation time.

3. Improved source description/definition and multi-portal irradiation setup

Unlike MCNP6, which cannot define the azimuthal angular distribution, and can only do a limited correlation in SDEF card to describe source information, i.e., energy, angle, space, and time domains, MANTA-Ray with COMPASS now can provide a multi-level correlation in source description, and a non-uniformed azimuthal angular distribution can be defined. In addition, user can build different profiles for different collimators and free-beam scenario. Furthermore, MANTA-Ray provides a user-friendly and useful function for multi-portal irradiations; it automatically generates calculation plan, as well as post-calculation display.

4. Medical images fusion

Physicians nowadays frequently use images fusion to define and contour tumor lesion by combining and comparing different medical images, e.g. MRI-CT or PET-CT. The intelligent fusion function in MANTA-Ray, not only reconstructs fused images with improved image quality, but also provides non-uniformed, in-vivo boron distribution by PET images. Moreover, it can combine CT images and physical/biological-weighted dose map, for user's convenience in viewing and conducting a plan assessment.

5. A built-in workflow chain for BNCT

Like most of the TPSs, MANTA-Ray is made for treatment plan creation and dose computation. Nonetheless, it also bridges treatment devices and peripheral equipment during treatment procedures. The prepared treatment plan can be passed to MUCS (Medical User Control System, controls the NeuPex™ AB-BNCT system) through Web protocol, and basing on the delivered plan, the patient positioning system could be enabled to place and position the patient by robot arm. When the positioning is done and confirmed, the MUCS will receive a confirmation before turning the beam on.

Estimation of external and internal exposure effects in consideration of internal activation during neutron irradiation in boron neutron capture therapy

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Purpose: It is expected that the accelerator-based boron neutron capture therapy (BNCT) will become widespread in near future. From the viewpoint of radiation protection and quality assurance for BNCT systems, it is important to estimate the exposure dose for patient due to BNCT irradiation. Particularly, thermal and/or epi-thermal neutron irradiation is performed on the patient, so that components constituting the body are possibly activated. There are some previous studies about the estimation for the exposure dose due to the in-vivo activation by animal experiments and simulations.[1],[2] These studies have suggested that the ^{24}Na and ^{38}Cl produced by the neutron activation have a significant effect on radiation exposure. The concentrations of ^{24}Na and ^{38}Cl are higher in blood than in body tissue. However, the previous studies do not consider of blood activation. In order to estimate the exposure dose more accurately, it is necessary to estimate the effects of external and internal exposure for the neutron activation in the body including blood.

Materials and methods: The external and internal exposure doses for normal tissues due to BNCT irradiation were estimated using a heavy ion beam transport calculation code "PHITS" and an internal exposure dose calculation code "DCAL".[3],[4] The radiation weighting factors and tissue weighting factors in ICRP pub. 103 were used.[5] Simulation calculations were performed for the typical BNCT studies for brain and head-and-neck tumors at a reactor-based BNCT system settled in Kyoto University Reactor (KUR). It was assumed that the concentrations of boron-10 in the normal tissues and blood were 25 ppm and the irradiation time was 1 hour. First, a phantom experiment was performed for estimating the normalization factors for the simulation results. Second, the external exposure doses were estimated using a computational phantom "MRKPs".[6] Third, the dose equivalent and the effective dose for the internal exposure due to the activation were estimated by DCAL, using the results for the radioactivity in the body by PHITS.

Results: For a case of the head-and-neck tumors, the equivalent dose due to the external exposure was almost 97 mSv on average for the whole body including the irradiated volume and its surrounding. Excepting the irradiated volume and its surrounding, the effective dose due to the external exposure was almost 11 mSv. The committed effective dose due to the internal exposure was almost 2.5 μSv (Table 1).

Conclusions: From the comparison with the references,[7] it was concluded that the results in this study were reasonable. The effect of the internal exposure due to the activation in BNCT on normal tissues was estimated to be four orders smaller than the external exposure. Therefore, it is not essential to consider about the internal exposure from the viewpoint of radiation protection, quality assurance, and daily treatment planning.

Nuclide	Effective Dose(Sv)	Percentage [%]
Na 24	8.7.E-07	34.8
Si 31	2.8.E-09	0.1
P 32	1.2.E-06	49.3
Cl 38	1.4.E-07	5.6
K 42	1.2.E-07	4.8
Ca 49	1.4.E-07	5.5
SUM	2.5.E-06	-

Table 1. *Committed effective dose and the percentage*

Keywords:

1.Internal exposure, 2.external exposure, 3.activation, 4.Monte Carlo simulation, 5.computational phantom

References:

[1] Sakurai Y, et al.. A feasibility study of the post irradiation dose estimation with SPECT technique for BNCT. Applied Radiation and Isotopes, 67, S218-221, 2019.
[2] Nakamura S, et al.. Evaluation of radioactivity in the bodies of mice induced by neutron exposure from an epi thermal neutron source of an accelerator based boron neutron capture therapy system. Proceedings of the Japan Academy. Series B, Physical and biological sciences, 93, 821-831, 2017.
[3] Sato T, et al.. Features of Particle and Heavy Ion Transport code System
[4] (PHITS) version 3.02. Journal of Nuclear Science and Technology, 55, 684-690, 2018.
[5] Eckerman K. F, et al.. User's Guide to the DCAL System. ORNL/TM 2001/190 Dist. Category UC 407, 2006.
[6] Recommendations of the International Commission on Radiological Protection 2007 (ICRP pub.103).
[7] Chansoo C, et al.. Mesh type reference Korean phantoms (MRKPs) for adult male and female for use in radiation protection dosimetry, Physics in Medicine and Biology, 64(8):085020, 2019.
[8] Fujiwara K, et al.. Induced radioactivity in the blood of cancer patients following boron neutron capture therapy. Journal of Radiation Research, 54, 769-774, 2013.

Dosimetry and treatment planning

Poster

P27

Gamma-ray dosimetry in the BNCT irradiation field using optically stimulated luminescence of BeO ceramics

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In the boron neutron capture therapy (BNCT), the dose is categorized into the boron dose, neutron dose and gamma-ray dose. These doses should be managed separately. The gamma-ray dosimetry in the BNCT irradiation field is required to evaluate only gamma-ray dose in an intense neutron field. Therefore, the dosimeter should have quite low neutron sensitivity. In addition, since the gamma-ray spectrum is difficult to be evaluated experimentally due to its high intensity, the energy response of the gamma-ray dosimeter is desired to be equivalent to the soft tissue. In some cases, the gamma-ray dose is evaluated using the dual ionization chamber system, in which the tissue-equivalent chamber and graphite-walled CO_2 gas chamber are used[1]. In other cases, the thermal stimulated luminescence (TSL) of BeO powder is used for routine dosimetry[2]. In the TSL measurement, in order to improve precision, a low heating rate is desired to be applied. This means that the precise measurement requires long measurement time.

In this study, we propose to apply the optically stimulated luminescence (OSL) of BeO ceramic for gamma-ray dosimetry in BNCT. Since BeO is composed of low-atomic-number and neutron-insensitive elements, it is ideal composition for a gamma-ray dosimeter used in a neutron dominant field. The BeO ceramic is additionally free from toxicity of BeO powder. The OSL can be faster and more precise than the TSL measurement.

We fabricated the home made OSL reader system and evaluated various performances of the BeO OSL dosimeter. We compared the OSL of BeO ceramic with the TSL of BeO powder and confirmed that the both results agree each other. We additionally measured radioactivity of the BeO ceramic irradiated with neutrons at the Heavy Water Neutron Irradiation Facility of the Kyoto University Reactor and confirmed that the ceramic have no neutron sensitive impurities.

K eywords:

gamma-ray dosimetry, optically stimulated luminescence, BeO ceramic

References:

[1] IAEA, IAEA-TECDOC-1223, Current status of neutron capture therapy, 2001.

[2] H. Tanaka, T. Takata, T. Watanabe, M. Suzuki, T. Mitsumoto, S. Kawabata, S. Masunaga, Y. Kinashi, Y. Sakurai, A. Maruhashi, K. Ono, Characteristic evaluation of the thermal neutron irradiation field using a 30 MeV cyclotron accelerator for basic research on neutron capture therapy, Nucl. Instruments Methods Phys. Res. Sect. A Accel. Spectrometers, Detect. Assoc. Equip. 983 (2020). https://doi.org/10.1016/j.nima.2020.164533.

Method of measuring high-LET particles dose

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In Boron Neutron Capture Therapy (BNCT), the total absorbed dose is the sum of four dose components with different RBE: boron dose; high-LET dose from the $^{14}N(n,p)^{14}C$ reaction ("nitrogen" dose); fast neutron dose; gamma-ray dose. *"The first two dose components cannot be measured in principle"*, as previously was written in [1, p. 279]. The methods for measuring the fast neutron dose for BNCT are absent also, as the energy of neutrons, as a rule, is obviously lower than 1 MeV and, for example, fission ionization chambers are not applicable. Quite a lot of proven approaches are existed only for measuring gamma-ray dose. We present a new approach for measuring boron dose, nitrogen dose and fast neutron dose in BNCT [2].

The idea of approach for measuring dose from high-LET particles is the following. The cell lines are exposed to g-radiation and mixed radiation (neutrons and g-radiation) measuring the dose of g-radiation. The doses of g-radiation which cause the same effect, for example cell surviving, are compared. The equivalent dose of high-LET particles was calculated by the formula: $D_n = D_{\gamma\ standard} - D_{\gamma\ mixed}$, where D_n – the equivalent dose of high-LET particles; $D_{\gamma\ standard}$ – the dose of g-radiation when the cells were exposed to g-radiation; $D_{\gamma\ mixed}$ – the dose of g-radiation when the cells were exposed to mixed radiation.

The work presents the results demonstrating the applicability of the new proposed approach for measuring the dose components due to neutrons: nitrogen dose, and fast neutron dose.

Keywords:
boron neutron capture therapy; absorbed dose; high-LET particles

References:

[1] W.A.G. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa (Eds.). Neutron Capture Therapy: Principles and Applications. Springer, 2012.
[2] I. Taskaeva, S. Taskaev. Method of measuring of dose produced by recoil nuclei. Patent for invention RU2743417 dated 18.02.2021.

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Response evaluation to gamma-ray of optical fiber-based neutron detectors using small pieces of Li-glass scintillator

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We are developing an optical fiber-based neutron detector as a real-time neutron monitor in an intense neutron field, such as BNCT. Our detector can be used in high spatial resolution measurements in a water phantom for QA of the neutron source for BNCT [1,2]. In the previous study [3], Li-glass scintillator was applied to the detector, and output linearity was confirmed even in a high counting rate of 450 kcps, which was nearly 9 times larger than the upper limit of the counting rate of the detector using LiF/Eu:CaF_2 eutectic scintillator. In the present study, to evaluate noise components in pulse height spectra of the detectors by gamma-ray contamination, the detector response to gamma-ray from ^{60}Co and ^{113m}Cd were evaluated.

The pulse height spectra obtained for thermal neutron and ^{60}Co gamma-ray at dose rate of 1.90, 3.68 and 7.50 Gy/h in the detector using the Li-glass scintillator with mass of 32 μg was shown in ***Figure 1***. Consequently, the gamma-ray counting rates for both of gamma-ray sources were found to be smaller than uncertainty associated with counting statistics in most applications where the neutron counting rate was expected to be larger than 1 kcps, and negligible at gamma-ray dose rate expected in BNCT neutron field (<1 Gy/h).

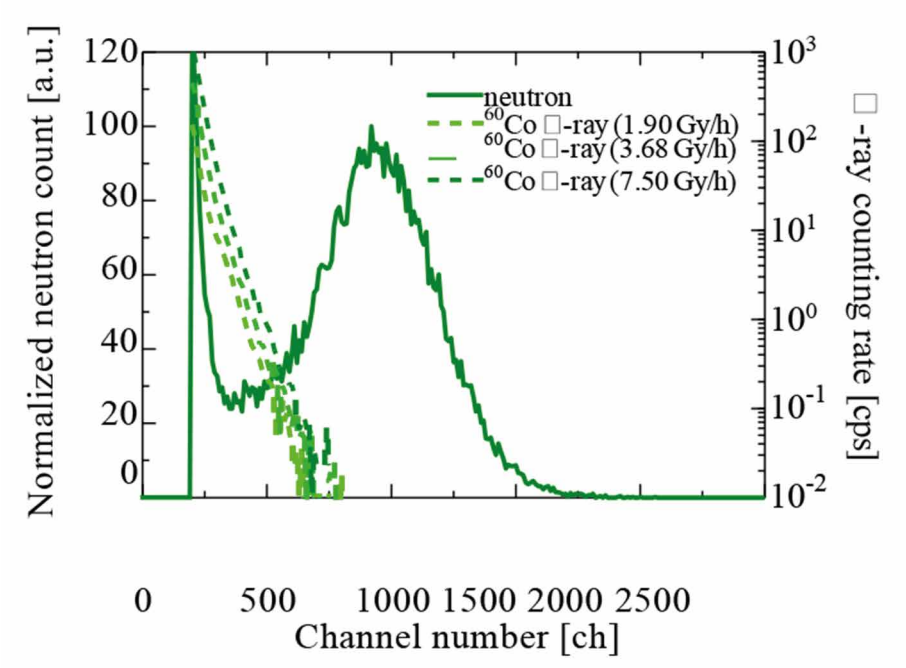

Figure 1. *The pulse height spectra obtained for thermal neutron and ^{60}Co gamma-ray in the detector using Li-glass scintillator with mass of 32 μg.*

Keywords:
optical fiber-based neutron detector, real-time neutron monitor, n-γ discrimination

References:

[1] K. Watanabe *et al*., Applied Radiation and Isotopes, Vol. 168, February 2021, 109553.
[2] A. Ishikawa *et al*., Radiation Measurements, Vol. 133, April 2020, 106270.
[3] A. Ishikawa *et al*., Sensors and Materials, Vol. 32, No. 4, April 2020, pp. 1489-1495.

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Examination of intra-fractional patient shift in boron neutron capture therapy

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Introduction

Boron neutron capture therapy (BNCT) is a type of radiation therapy that utilizes the nuclear reaction between thermal neutrons and boron nuclei (^{10}B) [1]. BNCT has been applied mainly to the patients suffering from head and neck cancer and malignant brain tumors using a neutron beam generated from research reactors. Usually, BNCT is finished at one session, while requiring irradiation time within a range of 30 to 60 minutes [2]. The purpose of this study is to investigate the intra-fractional patient shift from the set-up position during BNCT in which the patient was treated in a sitting position and the effect of the patient shift on the dose distribution in the tumor.

Materials and Methods

We analyzed the intra-fractional patient shift of the 13 consecutive patients of head and neck cancer or malignant brain tumors treated with BNCT in sitting position at Kyoto University Institute for Integrated Radiation and Nuclear Science. The radiotherapy irradiation field verification system was used to analyze the patient shift of each patient with referring to two computed radiographies taken at the set up and termination of BNCT session. To investigate the effect of the patient-shift on the dose distribution in the tumor, we made the parotid grand tumor model using the humanoid phantom.

Results

The intra-fractional patient-shift was ranged from -11 to 14 mm in anterior-posterior direction and from 1 to 15 mm in caudal direction, respectively. The change of the doses (maximum, mean, minimum) delivered to tumors per minutes were (-7.6%, -3.7%, 0.7%), (3.5%, -1.6%, -3.6%) and (2.2%, -6,6%, -13.4%) in cases of anterior, posterior and caudal shift in 15mm, respectively.

Conclusion

We analyzed the intra-fractional patient shift during BNCT treating the patients in sitting position and confirmed that, in case of head and neck cancer patients, the patient shifts caused substantial effect on the tumor dose distribution due to inhomogeneous distribution of the epi-thermal neutron field.

Keywords:
intra-fractional patient shift, head and neck cancer

References:

[1] Coderre JA, Morris GM. The radiation biology of boron neutron capture therapy. Radiat Res 1999; 151: 1-18.
[2] Kato I, Ono K, Sakurai Y et al. Effectiveness of BNCT for recurrent head and neck malignancies. Appl Radiat Isot 2004; 61: 1069-1073.

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γ-Ray Dose Measurement Using Radio-Photoluminescence Glass Dosimeter (RPLGD) in Neutron/γ-Ray Mixed Field for BNCT ~Examination of the response of RPLGD in low-energy region~

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In BNCT facility, since neutrons generate secondary γ-rays mainly by neutron capture reaction, the field becomes a mixed field of γ-ray and neutron. Hence, separate measurement of γ-ray and neutron is indispensable to control the exposure dose to the patient. In order to realize the separate measurement in the mixed field, we have proposed the "shielding filter method". This method uses two radiophoto-luminescence glass dosimeters (RPLGDs) and estimates the true γ-ray dose from the difference of measured two dosimeters covered with appropriate shielding filters. Currently, as the preliminary step, we use just one RPLGD covered with a γ-ray shielding filter, and examine whether it is possible to measure the γ-ray dose in a γ-ray field, not a mixed field. In the previous research, we designed an iron filter by using PHITS (Particle and Heavy Ion Transport code System) and conducted irradiation experiments with standard γ-ray sources. We found that we could measure γ-ray dose accurately in high-energy region, however in low-energy region, the measured absorbed dose rate was smaller than the calculated value of PHITS. We expected that the PHITS calculation overestimated the response of RPLGD in low-energy region. Therefore, in this research, we aim to obtain the accurate response of RPLGD in low-energy region. To do this, we use low-energy standard γ-ray sources,^{57}Co (14, 122, 136 keV), ^{109}Cd (22, 25, 88 keV), ^{241}Am (16, 60 keV). Since these γ-ray sources emit two or three energy photons, we use aluminum sheets of multiple thicknesses to try to make the photon energy monochromatic. For instance, in case of ^{57}Co, by using three types of aluminum sheets in thicknesses, 200, 500, 900 μm, the intensity ratio of the three monochromatic γ-rays (14, 122, 136 keV) can be changed. After that, by performing irradiation experiments three times, the response of RPLGD to γ-rays can be estimated. The concrete formula to be solved is shown in Formula 1. In Formula 1, A is the photon flux matrix that has pass through the aluminum sheets. Rows and columns are assigned to aluminum thickness and photon energy, respectively. is the response of RPLGD that we want to obtain. Also, is the absorbed dose rate of RPLGD we measure. By solving this equation using the Bayesian estimation method, we can obtain the response of the RPLGD. As a result of the series experiments, we found that it was difficult to obtain accurate response of RPLGD by using only standard γ-ray sources. This is probably because the number of γ-rays is too few to estimate the response correctly. In the next step, we used X-ray, because X-ray from an X-ray generator has a continuous spectrum. After doing X-ray irradiation, we were able to obtain the response of RPLGDs for enough points. In the future, by using the acquired response, we will design the γ-ray shielding filter appropriately to measure the γ-ray dose accurately in the γ-ray field, and finally, in the mixed field.

$$\begin{pmatrix} A_{200\mu m,14keV} & A_{200\mu m,122keV} & A_{200\mu m,136keV} \\ A_{500\mu m,14keV} & A_{500\mu m,122keV} & A_{500\mu m,136keV} \\ A_{900\mu m,14keV} & A_{900\mu m,122keV} & A_{900\mu m,136keV} \end{pmatrix} \cdot \begin{pmatrix} X_{14keV} \\ X_{122keV} \\ X_{136keV} \end{pmatrix} = \begin{pmatrix} B_{200\mu m} \\ B_{500\mu m} \\ B_{900\mu m} \end{pmatrix}$$

Formula 1. Formula to obtain the response of RPLGD in case of ^{57}Co

Development of Submillimeter Gamma Camera for Measuring Boron Distribution in Brain Tumor of Rat –Examination of one collimator hole camera–

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Recently, Boron Neutron Capture Therapy is regarded as a promising cancer therapy worldwide because of its low invasion characteristic and tumor cell selectivity. To develop and advance BNCT, one of the crucial problems to be solved is how to increase the boron drug accumulation in the tumor cell and develop the drug delivery system. Although accumulation of enough amount of boron is needed to gain the effectiveness of BNCT, it is not easy for currently available drugs such as BPA to accumulate sufficiently. Currently, we, therefore, administer in large doses in a short time. To solve this difficulty, especially in brain tumors, primary research is now underway, a boron cerebrospinal fluid administration using rats.

In our study, to examine the new method, we aim to develop a submillimeter gamma camera for measuring boron distribution in rats' brains. The gamma camera is the equipment for measuring a two-dimensional distribution of gamma-ray sources. Using the camera, we can directly measure the radioisotope-labelled boron distribution in the brain of small animals like rats in details. It is considered that this camera will be able to contribute to animal's BNCT in the future.

The first step in this study is to design the submillimeter gamma camera. The collimator and scintillator of the camera were determined by simulations using MCNP-5(A General Monte Carlo N-Particle Code). The gamma camera was designed to be able to see an object in submillimeter orders. A larger gamma-ray detection element was employed to suppress deterioration of the accuracy in observing such a small object. The area that the detector sees was narrowed down to about 1 mm square using the specially designed tapered collimator. The final target of the present study is to see a rat with a brain tumor. The measurements will be thus carried out by administering 18F-BPA, i.e., BPA labelled with a radioisotope, 18F, to confirm boron accumulation even in the tumor. In this study, what first set the design targets based on the dose and measurable radioactivity.

In the design, the number of collimator holes (number of detectors) was first set to one. Later, the number of holes was changed to two. This is because the number of free parameters to fix in the design was large (five in this case). By decreasing the number of collimator holes, the design values to be considered can be decreased. In the present study, as multiple collimators, the number was set to two, which is the minimum number of collimator holes to form a camera having multiple detectors. By performing simulations varying the parameters, the effects and trends were examined on the measured values and errors. We then finally determined the best parameters to achieve the target design values.

Until now, a prototype submillimeter gamma camera with a single collimator has been constructed, and the basic performance is confirmed using a standard gamma-ray source of 137Cs. We compare the measured results with the predicted values in the design. In the next step, we will increase the number of collimator holes to two (two detectors) to study the interference effect of multiple collimators. In the future, we will plan to measure a sliced sample of a rat brain directly.

Keywords:
Gamma Camera, Submillimeter, boron cerebrospinal fluid administration, BPA, brain tumor

References:

[1] reference in free format, include at least first author, journal, volume, pages and year

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Feasibility study on energy-dependent neutron flux monitor using multi-core SOF detector

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[3] *Graduate School of Biomedical Science and Engineering*

1. Background

Boron Neutron Capture Therapy (BNCT) is a radiation cancer treatment that uses energy generated by the nuclear reaction between boron and neutrons. In recent years, BNCT treatment using an accelerator has come to a feasible stage. Since BNCT treatment using an accelerator contains a large amount of epithermal neutron components, it is difficult to evaluate the amount of neutron irradiation using a gold activation method as in the past. In order to evaluate thermal neutron flux during BNCT irradiation, we have developed a SOF detector (Scintillator with Optical Fiber Detector) [1,2] for measuring thermal neutron flux in real time, and reported on the usefulness of real time measurement in clinical[3,4]. The SOF detector uses nuclear reaction energy by neutron sensitizers, but the energy response differs depending on the nuclide of the neutron sensitizer. We aim to develop a new neutron energy spectrometer that can simultaneously evaluate thermal, epithermal, fast neutrons, and gamma dose by using multi-core type SOF detector which consists of some scintillators with different neutron sensitizers.

2. Materials and Methods

Nuclides of ^{6}Li, ^{10}B, ^{14}N and ^{32}S were selected as the neutron sensitizers for the SOF detector as a result of selecting a nuclear reaction with a large reaction block and a large estimated emission amount in the scintillator from the nuclear data library JENDL-4.0. A fundamental study of a cylindrical spectrometer using a SOF detector was conducted using the particle transport Monte Carlo calculation code PHITS ver. 2.8.1. SOF detectors were placed at 5 mm intervals on the central axis of an acrylic cylindrical water phantom measuring 18 cm in diameter and 20 cm in length, and a system was created to measure a total of 38 locations. In this research, we implemented an unfolding algorithm based on the ML-EM method. Since the spectrum estimation by the unfolding method requires a response function for mono-energy neutron, the response function was calculated using PHITS. The energy range of the created response function was from 1 meV to 10 MeV, and neutron energy spectrum estimation was performed using a pencil beam of 30 mono-energy neutrons.

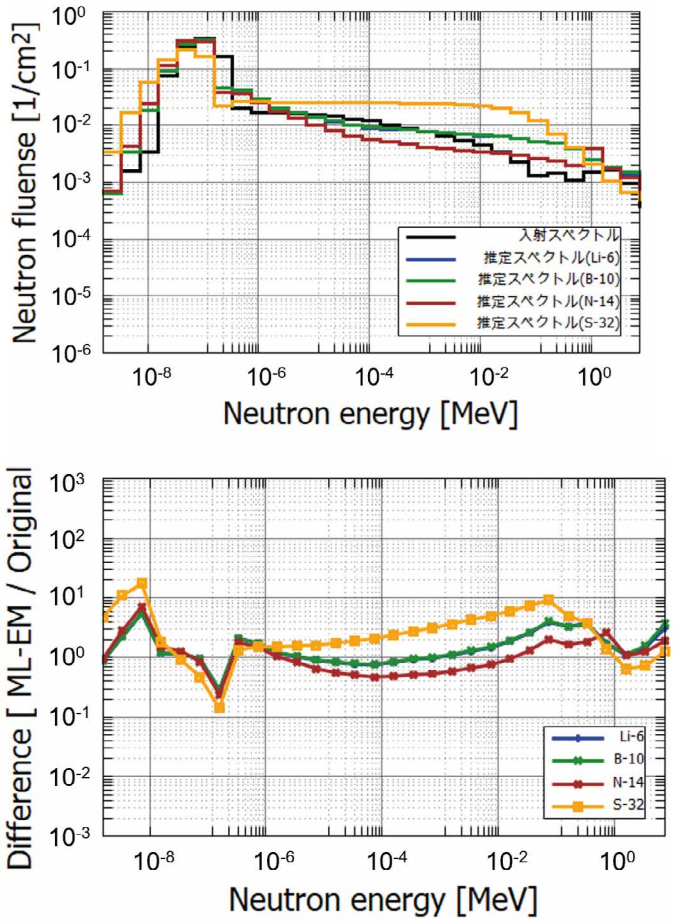
3. Results and Discussions

Figure 1 shows the estimated neutron energy spectrum at the surface of the water phantom in case of irradiating by thermal-epithermal mixed neutron energy irradiation mode at KUR. From the result of the estimated neutron energy spectra, it was confirmed to be possible to estimate the spectrum with relatively high accuracy by using nuclides of ^{6}Li, ^{10}B and ^{14}N. In addition, from the facts that the order of the reaction cross section is ^{10}B > ^{6}Li > ^{14}N and the order of light emission in the plastic scintillator is ^{6}Li >> ^{14}N > ^{10}B, ^{6}Li has an advantage as a sensitizer for SOF detectors at present stage. However, it was shown that neutron energy spectrum estimation is possible for other nuclides.

4. Conclusions

As a result of neutron energy spectrum estimation using a single nuclide, it was confirmed to be possible to estimate the spectrum with relatively high accuracy by using nuclides of ^{6}Li, ^{10}B and ^{14}N. As future work, we will

improve the accuracy of estimating neutron energy spectrum using the multi-core SOF detector that combines these nuclides.



(a) Estimated neutron energy spectra (b) Difference from the ground truth

Figure 1. *Neutron energy spectra comparison for thermal-epithermal mixed neutron energy irradiation mode*

Keywords:
multicore-SOF detector, irradiation field measurement, neutron energy spectrometer, real-time neutron flux monitor

References:

[1] M. Ishikawa et al., "Development of real-time thermal neutron monitor using boron-loaded plastic scintillator with optical fiber for Boron Neutron Capture Therapy," Applied Radiation and Isotopes 61-5, pp.775-779, 2004.
[2] M. Ishikawa et al., "Development of a Wide-Range Paired Scintillator with Optical Fiber Neutron Monitor for BNCT Irradiation Field Study," Nucl. Instr. Meth. A551, pp.448-45, 2005.
[3] M. Ishikawa et al., "Application of an ultraminiature thermal neutron monitor for irradiation field study of accelerator-based neutron capture therapy," Journal of Radiation Research 56, pp. 391-396, 2015
[4] M. Ishikawa et al., "Early clinical experience utilizing Scintillator with optical fiber (SOF) detector in clinical boron neutron capture therapy: Its Issues and solutions," Radiation Oncology 11:105, DOI: 10.1186, 2016.

P106

Evaluation Method of Radioactivation and Neutron Absorption of Dental Prosthesis on NCT and Countermeasures for these adverse events

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Kubota Dental Clinic Medical Corporation

On NCT, radioactivation evaluation and neutron absorption evaluation of the elements and nuclides that make up the human body are already completed. But for dental prostheses many elements that do not normally exist in the human body are used.

The author examined a method for evaluating radioactivation and neutron absorption of dental materials on NCT. For more accurate evaluation, it is better to connect the shape and composition of the dental prosthesis to the Monte Carlo simulation at the time of irradiation planning and calculate at the same time, but since it is complicated and difficult. Therefore, as a guide, we devised an evaluation method for radioactivation and neutron absorption by capturing neutrons using the thermal neutron reaction cross section Maxwellian

As a rough estimate, it was found that dental gold alloys, cobalt-chromium alloys, zirconia ceramics, etc. were radioactivated to a non-negligible level, and that they could absorb neutron beams and diminish the therapeutic effect. Therefore, as a countermeasure, it was considered better to remove the dental prosthesis once before irradiation. In addition, it was considered that the degree of radioactivation of the pure titanium implant fixture was low and it was not necessary to remove it.

Keywords:
dental, prostesis, radioactivation, neutron absorption, evaluation, dental materials.

Measurement of the 14N(n,p) reaction at n_TOF (CERN) for BNCT dose calculations

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In BNCT, an accurate determination of the dose in the different tissues is a paramount input for treatment plannings. To this aim, a proper knowledge of the cross-section of the neutron induced reactions is strongly desired. In this sense, reducing the uncertainty in dose calculations during treatment planning is important for the determination of the dose at the organs of risk. Among others, nitrogen is an element of key relevance in BNCT, producing a major contribution to the dose in normal tissue from low energy neutrons. There is a 5% discrepancy between the ENDF and JENDL evaluations at thermal energy. Considering experimental data, higher differences are present, with some of them in disagreement with the evaluations. At higher energies in the keV region and above, the experimental data do not match well with the extrapolations from the thermal energy. These discrepancies can produce deviations of up to a 10% in the total dose delivered to healthy tissue.

For these reasons, a measurement of the 14N(n,p) reaction cross-section was carried out at the neutron time of flight (n_TOF) facility of CERN [1], in order to measure the cross-section covering the epithermal range from below thermal energy. Thin adenine foils were used in order to overcome the challenge of detecting the protons generated at the reaction due to their relatively low energy. Two independent setups were used for the measurement, one of them based on MicroMegas detectors and the other on Double-Sided Silicon Strip Detectors (DSSSD). The MicroMegas setup was placed inside the beam profiting from its high neutron transparency and large geometrical efficiency. DSSSD were placed off-beam, with reduced background, in order to extend the energy range covered by this measurement. Preliminary results of the cross-section measured will be shown.

Keywords:
Cross-Section measurement, n_TOF, nitrogen, dose uncertainties

References:

[1] J. Praena, I. Porras, M. Sabaté-Gilarte, F. Ogállar, P. Torres-Sánchez, C. Lederer-Woods, T. Davinson, M. Dietz, S.J. Lonsdale, P.J. Woods, M. Barbagallo, J. Andrzejewski, J. Perkowski, S. Cristallo, C. Abia, F. Arias de Saavedra, *et al* n_TOF collaboration. *The 14N(n,p)14C and 35Cl(n,p)35S reactions at n_TOF-EAR2: dosimetry in BNCT and astrophysics.* CERN Document Server: proposal CERN-INTC-2017-039/INTC-P-510: https://cds.cern.ch/record/2266484/.

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Out-of-field dose study in accelerator-based boron neutron capture therapy

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In this work we have carried out the study of the out-of-field dose in boron neutron capture therapy (BNCT). Our description is focused on a new neutron production system based on a low-energy neutron accelerator, by means of a beam shaping assembly (BSA) designed by the UGR [1] for its use in the subsequent simulations for the characterization of the dose outside the field. All the simulations carried out in this work are programmed in Monte Carlo, specifically in MCNPX [2].

This dose has been quantified using physical and biological criteria, and the possible extrapolation of the restrictions for other forms of radiotherapy to BNCT has been studied. From this study it is concluded that the accelerator-based BNCT meets the criteria on the equivalent dose outside the field established for photon and ion therapies, produces an acceptably low effective dose to the whole body in the patient in the treatments of brain tumors, and some criteria are proposed for limiting the leakage radiation of the equipment.

The total effective dose rate that the whole body receives when applying this therapy does not exceed 1.5 mSv/min. In this work we will show results for the effective dose in all the relevant organs, calculated with an anthropomorphic phantom.

Keywords:

BNCT, neutrons, accelerator, dose, radiation protection.

References:

[1] P. Torres-Sanchez, I. Porras, N. Ramos-Chernenko, F. A. D. Saavedra, and J. Praena, "Optimized beam shaping assembly for a 2.1-MeV proton-accelerator-based neutron source for boron neutron capture therapy," *Scientific Reports*, vol. 11, p. 7576, 123. https://rdcu.be/ciei4

[2] D. B. Pelowitz, MCNPX TM *User's Manual,Version 2.5.0, California, Los Alamos,* 2005.

Feasibility study of accelerator-based BNCT of liver metastases without liver extraction

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In this work, a feasibility study of a treatment for liver metastases from colon cancer by external irradiation with accelerator-based BNCT has been carried out. This was done through simulations using an anthropomorphic model and the particle transport Monte Carlo code MCNP in its latest version (MCNP6) [1]. A source of neutrons moderated to energies in the epithermal range (energy between 0.5 eV and 10 keV) was used by means of a Beam Shaping Assembly (BSA) developed by the research team of the University of Granada [2].

A study was made of the optimal position at which the highest equivalent biological dose rate was found in the tumor. For the calculation of the equivalent biological dose rate, the weight of each physical dose was taken into account with currently used weighting factors. The values of the boron uptake with the compound boronophenylalanine (BPA) were assumed from the patient data from the clinical trials performed in Pavia [3]. For the boron uptake in the many organs at risk in the abdomen, a estimation was done from the scarce studies of biodistribution of 18F-BPA found in the literature [4].

It was found that the tumor received a much higher biological dose equivalent rate than the other tissues, and that the position of the beam, seems not as critical as in other forms of radiotherapy. The dose received in a single session delivering 30 Gy-eq to the tumor by all organs at risk was found to be well below the maximum tolerable values in standard radiotherapy procedures.

Keywords:

BNCT, Monte Carlo simulation, liver metastases.

References:

[1] C.J. Werner. MCNP USER'S MANUAL. Code Version 6.2. October 27, 2017.

[2] Torres-Sánchez, P., Porras, I., Ramos-Chernenko, N. Arias de Saavedra F., Praena J. Optimized beam shaping assembly for a 2.1-MeV proton-accelerator-based neutron source for boron neutron capture therapy. Sci Rep 11, 7576 (2021).

[3 Zonta, A., Pinelli, T., Prati, U., Roveda, L., Ferrari, C., Clerici, A. M., Zonta, C., Mazzini G., Dionigi, P., Altieri, S., Bortolussi, S., Bruschi, P., Fossati, F. Extracorporeal liver BNCT for the treatment of diffuse metastases: What was learned and what is still to belearned. Applied Radiation and Isotopes, 67(2009), 67–75.

[4] Sakata, M., Oda, K., Toyohara, J., Ishii, K., Nariai, T., Ishiwata, K. Direct comparison of radiation dosimetry of six PET tracers using human whole-body imaging and murine biodistribution studies. Ann Nucl Med. 2013 Apr;27(3):285-96.

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