The 17th International Congress on Neutron Capture Therapy

University of Missouri
Columbia, Missouri, USA

ABSTRACTS FOR PRESENTATION

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Welcome Address

Dear Colleagues,

It is my pleasure to welcome everyone to the 17th International Congress on Neutron Capture Therapy (ICNCT-17) at the University of Missouri located in the heartland of America. The congress will be spread over five days and will feature plenary talks, poster presentations and focused sessions in the clinical, radiobiological and neutron physics aspects of Boron Neutron Capture Therapy (BNCT).

Clinicians and researchers from around the world come together to showcase their findings and generate new thoughts related to Neutron Capture Therapy. The key areas include the latest developments in accelerator-based neutron sources, the next generation of delivery agents, as well as the latest results in chemical, biological and clinical research.

I am proud to be a part of this global community composed of world-renowned scientists from industry and academia collaborating in pursuit of a common goal, a cancer cure. There is no better time than now, as we look forward to the exciting future for BNCT. With a number of promising developments currently underway, from new boron delivery agents to new accelerator-based neutron sources, the promise of BNCT as a standard radiation therapy for cancer is finally becoming a reality.

On behalf of the University of Missouri and the International Institute of Nano and Molecular Medicine I am delighted to welcome you to this beautiful campus in the heart of the United States.

Satish S. Jalisatgi, Ph.D.

President, 17th ICNCT meeting
President, International Society for Neutron Capture Therapy
Assistant Director, International Institute of Nano and Molecular Medicine
University of Missouri

Dear Colleagues,

With a great sense of satisfaction, I am pleased to welcome the participants of the 17th International Congress on Neutron Capture Therapy (ICNCT) convened by the International Institute of Nano and Molecular Medicine (I^2NM^2) of the University of Missouri (MU), Columbia. As in the past, this congress collects a diverse group of scientific contributors for the purpose of defining the current state of neutron capture therapy and plans for future medical advances.

The I^2NM^2 was founded in 2005 when the Hawthorne research group relocated from the University of California Los Angeles (UCLA) to MU. This move was possible due to the construction of a dedicated I^2NM^2 building at MU. In addition, the nuclear reactor at MU was equipped with a thermal neutron beamline suitable for BNCT studies with small animals. Boron chemistry relevant to BNCT was emphasized at MU along with the associated biological aspects of research leading to small animal therapy studies.

Besides exploratory BNCT studies the I^2NM^2 research program has involved several areas based upon borane/carborane chemistry. These are drug delivery (closomers), new routes to ^{10}B enriched compounds for use in BNCT, new MRI agents for tumor visualization, hydrogen storage with boranes and molecular motors based upon metallacarboranes.

Members of the I^2NM^2 are especially pleased by our opportunity to host the 17th ICNCT since we are intimately involved in BNCT chemistry and biology.

With a warm welcome to all,

M. Frederick Hawthorne

Fred Hawthorne, Ph.D.
Director, International Institute of Nano and Molecular Medicine (I^2NM^2)
University of Missouri

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Thomas Everett
Elizabeth Porting-Jackson
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Erica Lovercamp
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1994-2016 Hatanaka Award Recipients

1994, 6th ICNCT, Kobe, Japan
Jeffrey Coderre (USA)

1996, 7th ICNCT, Zurich, Switzerland
Yoshinori Yamamoto (Japan)

1998, 8th ICNCT, LaJolla, USA
Borje Larsson (Sweden)

2000, 9th ICNCT, Osaka, Japan
Detlef Gabel (Germany)

2002, 10th ICNCT, Essen, Germany
Yoshinobu Nakagawa (Japan)

2004, 11th ICNCT, Boston, USA
Rolf Barth (USA)

2006, 12th ICNCT, Takamatsu, Japan
David Nigg (USA), Wolfgang Sauerwein (Germany)

2008, 13th ICNCT, Florence, Italy
Otto Harling (USA)

2010, 14th ICNCT, Buenos Aires, Argentina
Tooru Kobayashi (Japan), Akira Matsumura (Japan), Koji Ono (Japan)

2012, 15th ICNCT, Tsukuba, Japan
Raymond Moss (Netherlands)

2014, 16th ICNCT, Helsinki, Finland
Shin-Ichi Miyatake (Japan)

2016, 17th ICNCT, Columbia, Missouri, USA
Heikki Joensuu (Finland)

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International Institute of Nano & Molecular Medicine

KEYNOTE SPEAKERS

Invited Speakers

Keynote/Plenary Speakers

Rolf F. Barth, M.D.

Academy Professor, Department of Pathology, The Ohio State University

My research interests in BNCT began in 1979 when, upon joining the Department of Pathology at The Ohio State University, I met Albert Soloway, Ph.D., one of the pioneering boron chemists who had focused their attention on the design and synthesis of new boron delivery agents that potentially could be used clinically. Over the following years we have worked together closely to design, synthesize, and evaluate a variety of boron compounds. My own major research interests have included 1) using the F98 rat glioma model to optimize the delivery and dosing paradigms of the two boron compounds, sodium borocaptate and boronophenylalanine, which have been used clinically to treat patients with brain tumors; 2) the design, synthesis, and evaluation of two molecular targeting agents: boronated monoclonal antibodies directed against the epidermal growth factor receptor (EGFR) using genetically engineered F98 glioma cell lines; and, together with Dr. Werner Tjarks, carboranyl thymidine analogues that specifically target thymidine kinase 1 expressing tumors; and 3) together with Drs. Subhash Chandra and George Kabalka, evaluating unnatural boron-containing amino acids as potential delivery agents for BNCT of brain tumors and melanomas. Over the past 8 years a new line of investigation has focused on another approach for the treatment of brain tumors, combining intracerebral convection enhanced delivery of carboplatin or cisplatin with X-irradiation, again using the F98 glioma model.

Dr. Silva Bortolussi

National Institute of Nuclear Physics (INFN), Unit of Pavia, Italy

I have worked in BNCT since my M.Sc. thesis in 2003. I have participated in the clinical treatment of ex-situ liver BNCT: the organ affected by multiple metastases was explanted after BPA treatment, irradiated in the thermal column of the TRIGA reactor of University of Pavia and re-implanted in the patients. Afterwards, I dedicated to the feasibility study of BNCT for the disseminated tumours of the lung and for limb osteosarcoma, using multiple external epithermal neutron beams. Presently I work in the project to establish a BNCT clinical facility in Italy based on a Radio Frequency Quadrupole accelerator coupled with a beryllium target.

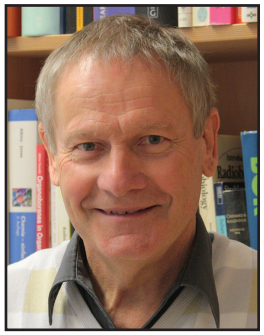
Prof. Vladimir Bregadze

A.N.Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences

Professor Vladimir Bregadze is a Head of Laboratory of Organoaluminum and Boron Compounds of A.N.Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences. His fields of interest are organic and inorganic derivatives of Boron and Main Group metals, chemistry of polyhedral boranes and carboranes, study of their reactivity and application in medicine and for design of materials. He published over 400 research papers, reviews and chapters in books. V.I.Bregadze twice received State Prizes in Science and

Technology for “Development and Application of New Materials in Industry”, and for “Chemistry of Carboranes and Polyhedral Boranes”. He is Member of the Editorial Boards of “Russian Chemical Bulletin”, International Journals “Main Group Chemistry” and “Biochemical and Biomedicinal Journal of Cancer Research”, Member of the International Committees of the International and the European Meetings on Boron Chemistry (IMEBORON and EUROBORON). V.I.Bregadze is Adjunct Professor of Beijing University of Chemical Technology. He was invited speaker at several IMEBORON, EUROBORON and Organometallic Conferences, Lecturer in Universities of Belgium, China, Germany, India, Japan, France, Poland, Portugal, Sweden and USA in 1988-2015.

Detlef Gabel



Wisdom Professor of Chemistry, Department of Life Sciences and Chemistry, Jacobs University, Bremen, Germany

Use of boron cluster compounds in medicine and material sciences; dyes as modulators of biological effects of toxic agents

Narayan S. Hosmane, PhD.

FRSC, Distinguished Research Professor, Northern Illinois University

Much of Dr. Hosmane’s research centers on the development of nano-structured boron and gadolinium compounds for boron and gadolinium neutron capture cancer therapies (BNCT and GdNCT). Compounds his research group has synthesized in laboratories are being utilized in clinical trials in Japan. Dr. Hosmane collaborates with Argonne and Fermilab in addition to working with Kishwaukee Hospital and DeKalb Clinic on prostate and bladder cancer research.

Andres J. Kreiner

Professor of Physics; Superior investigator at Atomic Energy Commission of Argentina (CNEA) and National Research Council; Head Department of Accelerator Technology and Applications at CNEA

Application of Nuclear Physics-based techniques to Biomedical, Environmental and Materials Science problems. Development of accelerator technology. Long standing involvement in BNCT.

George E. Laramore, PhD, MD

Peter Wootton Professor of Radiation Oncology, Department of Radiation Oncology, University of Washington in Seattle

George Laramore is the Peter Wootton Professor of Radiation Oncology at the University of Washington. He holds a Ph.D in physics from the University of Illinois and an M.D. from the University of Miami. He is board certified in Therapeutic Radiology and Radiation Oncology and served as department

chair between 1997-2013. He was the founding medical director for the Seattle Cancer Care Alliance Proton Center and has been the medical director for the University of Washington Fast Neutron Radiotherapy Center since 1978. His primary research interests lie in the interface between physics and medicine with particular emphasis on the role of high linear energy transfer (LET) particle radiation in treating human malignancies. He has been involved both with conventional BNCT and in the use of BNCT to boost the efficacy of fast neutron radiotherapy. Another area of interest is the use of 211At and other -emitters for targeting disseminated tumors and for bone marrow transplantation. He has chaired many clinical trials conducted by the Radiation Therapy Oncology Group (RTOG) with special emphasis on the treatment of head and neck cancer and is on the Board of Directors for the Proton Collaborative Group (PCG).

Akira Matsumura M.D., Ph.D.

Vice-president, University of Tsukuba; Director, University of Tsukuba Hospital; Chairman and Professor, Department of Neurosurgery; Faculty of Medicine, University of Tsukuba

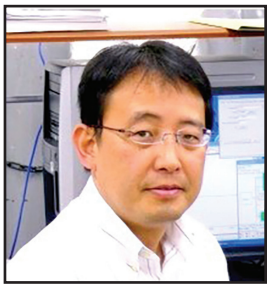
Clinical and basic research on BNCT applied to malignant brain tumor development of accelerator based in-hospital BNCT.

Shin-Ichi Miyatake

Professor, Cancer Center, Osaka Medical College

Treatment of malignant brain tumors, including as follows a) BNCT for malignant gliomas, high grade meningiomas b) Principal investigator for accelerator based BNCT clinical trials for recurrent malignant gliomas c) Principal investigator for nationwide prospective multicenter clinical trial of bevacizumab for patients with symptomatic brain radiation necrosis, supported by Japanese FDA

Hiroyuki Nakamura



Professor, Tokyo Institute of Technology

My research interests include synthetic methodology, medicinal chemistry, chemical biology, photodynamic therapy, and neutron capture therapy.

Mandy Schwint

PhD in Biological Sciences, Head Radiation Pathology Division, Department of Radiobiology, Comisión Nacional de Energía Atómica, Argentina

Principal Investigator of the project “Experimental Boron Neutron Capture Therapy (BNCT) studies for the treatment of oral cancer and precancer, liver metastases, lung metastases and rheumatoid arthritis” from 1998 to date. My research interests are radiobiology, BNCT radiobiology, translational studies in in vivo animal models and preclinical studies.

DAILY PROGRAM

Sunday, October 2, 2016

Donald W. Reynolds Alumni & Visitor Center

3:00 pm - 4:00 pm
Executive Board Meeting

4:00 pm - 4:30 pm
Board of Councilors Meeting

4:30 pm - 6:00 pm
Registration & Check-in

4:30 pm - 7:00 pm
Exhibits

4:30 pm - 7:00 pm
Networking Reception

Monday, October 3, 2016

Donald W. Reynolds Alumni & Visitor Center

8:00 am - 9:00 am
Registration & Check-in

8:00 am - 6:15 pm
Exhibits

9:00 am - 9:30 am
Opening Ceremony

9:30 am - 10:15 am
Hatanaka Lecture
Heikki Joensuu, Helsinki University Central Hospital, Finland

10:15 am - 10:35 am
Break

PLENARY SESSION 1

10:40 am - 12:15 pm | Columns Ballroom

10:40 am - 11:00 am
Tumor Selection for BNCT: A Clinician's Perspective
George Laramore, Department of Radiation Oncology, University of Washington, Seattle, USA

11:05 am - 11:25 am
Requalification and Experimental Validation of the Epithermal Neutron Beam Facility for Radiotherapy Research at Washington State University
David Nigg, Idaho National Laboratory, USA

11:30 am - 11:50 am
New Gadolinium Agents for Binary Cancer Therapies
Louis Rendina, The University of Sydney, Australia

11:55 am - 12:15 pm
Molecular Targeting of Boron Delivery Agents for Neutron Capture Therapy of Brain Tumors in the Genomic Era
Rolf F. Barth, Department of Pathology,The Ohio State University, USA

12:15 pm - 1:15 pm
Lunch

PLENARY SESSION 2
1:30 pm - 3:05 pm | Columns Ballroom

1:30 pm -1:50 pm
Worldwide Status of Accelerator-Based BNCT
Andres Kreiner, Atomic Energy Commission of Argentina (CNEA) and National Research Council, Argentina

1:55 pm - 2:15 pm
Extra-corporal BNCT for liver malignancies: Lessons learnt from 'Liver Purge'
Matthias Blaickner, Health and Environment Department, AIT Austrian Institute of Technology GmbH, Austria

2:20 pm - 2:40 pm
Production of ^{10}B-enriched materials at the International Institute of Nano and Molecular Medicine, University of Missouri-Columbia, USA
Alexander Safronov, University of Missouri International Institute of Nano & Molecular Medicine, USA

2:45 pm - 3:05 pm
Accelerator-based neutron source for boron neutron capture therapy: *in vitro* efficacy evaluation with in-sample dosimetry using gold nanoparticles
Alex Zaboronok, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Japan

3:05 pm - 3:25 pm
Break

PLENARY SESSION 3
3:30 pm - 5:05 pm | Columns Ballroom

3:30 pm - 3:50 pm
Optimization of treatment procedure for hospital-installed accelerator-based BNCT: The experience of Southern Tohoku BNCT Research Center
Katsumi Hirose, Southern Tohoku BNCT Research Center, Japan

3:55 pm - 4:15 pm
A Dose Response Analysis of Head and Neck Cancer Patients Treated with Boron Neutron Capture Therapy (BNCT) in Finland
Hanna Koivunoro, Neutron Therapeutics, Finland

4:20 pm - 4:40 pm

Enhanced Permeability and Retention (EPR) Effect-Based Efficient Boron Delivery Systems for BNCT

Hiroyuki Nakamura, CLS, Institute of Innovative Research, Tokyo Institute of Technology, Japan

4:45 pm - 5:05 pm

Feasibility and efficacy of Boron Neutron Capture Therapy for diffused lung tumors: the Pavia University experience on the animal model

Ian Postuma, University of Pavia, National Institute of Nuclear Physics (INFN), Italy

5:15 pm - 6:15 pm

Small Committee Meetings

POSTER SESSION 1

5:15 pm - 6:15 pm | Great Room

1. **Mechanism of Action Analysis for Boric Acid-Mediated Neutron Capture Therapy of Cancer**
   Yu-Chi Bai, Department of Medical Science & Institute of Bioinformatics and Structural Biology, National Tsing Hua University, Taiwan
2. **FBPA-PET predicts L-BPA concentration after amino acid preloading in HuH-7 liver tumor model**
   Matthias Blaickner, Health and Environment Department, AIT Austrian Institute of Technology GmbH, Austria
3. **Adaption of a pin-diode detector as an online neutron monitor for the thermal column of the TRIGA research reactor**
   Matthias Blaickner, Health and Environment Department, AIT Austrian Institute of Technology GmbH, Austria
4. **Analysis of Biological and Physical Markers as Prospective Indicators of Tumor Response for the Individualized BNCT Treatment in a Melanoma Animal Model**
   Marina Carpano, National Atomic Energy Commission (CNEA), Argentina
5. **Using Low-dose Gamma Radiation to Improve the Therapeutic Efficiency of BPA-mediated BNCT in an Orthotropic Oral Cancer Animal Model**
   Fong-In Chou, Nuclear Science and Technology Development Center, National Tsing Hua University, Taiwan
6. **Theoretical approach based on Monte Carlo simulations to predict the cell survival following BNCT**
   Daniel Santos, LPSC, Grenoble-Alpes University, CNRS-IN2P3, France
7. **BSH delivery by angiopep-2 modified liposome and gene expression variation in glioma cells treated by an In-Hospital Neutron Irradiator**
   Bin Feng, Dalian Medical University, China
8. **BNCT mediated by boric acid is selectively effective in tumors in the hamster cheek pouch oral cancer model**
   Marcela A. Garabalino, National Atomic Energy Commission (CNEA), Argentina

9. **Development of TSPO ligand as a target compound for boron neutron capture therapy: tumor imaging potential with PET**
   Md. Maqusood Alam, Neuroscience Research Institute, Gachon University, South Korea

10. **Effect of particle size of nanopaticulate L-BPA formulation on biodistribution of ^{10}B after its subcutaneous administration to tumor-bearing mice**
    Tooru Andoh, Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University, Japan

11. **Development of Fluorescent Iron Oxide - Gadolinium Borate Multifunctional (Fe_3O_4@ $GdBO_3$/SiO_2(FITC)-FA) Nanocomposites for Combined Gadolinium and Boron Neutron Capture Therapy (GdBNCT)**
    Okan Icten, Hacettepe University, Turkey

12. **Boron Neutron Capture Therapy (BNCT) for Axillary Lymph Node Metastasis of Breast Cancer**
    Takuya Fujimoto, Hyogo Cancer Center, Department of Orthopedics Surgery, Japan

13. **Boron neutron capture therapy in non-SCC patients with intractable head and neck malignancies who have no other treatment options**
    Itsuro Kato, Department of Oral and Maxillofacial Surgery, Osaka University Graduate School of Dentistry, Japan

14. **Design and Feasibility of a Gamma-Ray Detection System for Three Dimensional Patient Dose Imaging**
    Kiyotaka Akabori, Sumitomo Heavy Industries, Ltd., Japan

15. **An innovative neutron spectrodosimeter based on thermal and fast neutron bubble detectors**
    Katia Alikaniotis, University of Trieste, Italy

16. **Deuteron Induced Reactions as Epithermal Neutron Sources for Accelerator-Based Boron Neutron Capture Therapy**
    Maria Eugenia Capoulat, National Atomic Energy Commission (CNEA), National University of General San Martín, The National Scientific and Technical Research Council (CONICET), Argentina

17. **Blistering Characteristics of Backing Metals for AB-BNCT Neutron-Producing Target by Low-Energy Hydrogen Ion Implantation**
    Der-Sheng Chao, Nuclear Science and Technology Development Center, National Tsing Hua University, Taiwan

18. **Cancericidal Nuclide Neutron Knife**
    Chen Xinru, China National Nuclear Corporation/China Zhongyuan Engineering Corporation, China

19. **Comparison of Dose Calculation Using Treatment Planning Systems THORplan and SERA for BNCT**
    Yi-Chiao Teng, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan

20. **ABENS-BNCT System: Verification of durability of thin layer solid lithium target for high current proton beam**
Ryo Fujii, Cancer Intelligence Care Systems, Inc., Japan

21. **Fricke Gel Detectors In High-LET and Long-Time Irradiations for BNCT Dosimetry**
Grazia Gambarini, The University of Milan, Department of Physics, Italy

22. **Response of Fricke Gel Detectors to Extended and High-LET Irradiations in BNCT Beams**
Grazia Gambarini, The University of Milan, Department of Physics, Italy

23. **"Neobor"— European/International Scientific Network for BNCT Research and Medical Training at MARIA Reactor (Poland)**
Michal Gryzinski, National Center for Nuclear Research, Poland

24. **Clinical Commissioning of a Cyclotron-Based Epithermal Neutron Source at Southern Tohoku BNCT Research Center**
Takaomi Harada, Southern Tohoku BNCT Research Center, Japan

25. **Preliminary Study for the Beam Component Separation Using Polymer Gel Detector Containing Lithium Compounds**
Shin-ichiro Hayashi, Hiroshima International University, Japan

26. **Dynamic Infrared Imaging in the Hamster Cheek Pouch Model of Oral Cancer: Searching for prognostic parameters of tumor response and normal tissue radiotoxicity in BNCT**
Maria Herrera, National Atomic Energy Commission (CNEA), Argentina

27. **Optimum Design of an Electron-Linear-Accelerator-Driven Subcritical Neutron Multiplier for Boron Neutron Capture Therapy**
Fujio Hiraga, Hokkaido University, Japan

28. **Upgrade of On-line Monitoring System of BNCT Beam at THOR**
Yu-Hsiang Huang, National Tsing Hua University, Taiwan

29. **Neutron Activation Analysis Using BNCT Beam at THOR**
Chun-Kai Huang, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan

30. **The Design for BNCT Facility Based on Radiation Dose Estimation**
Go Ichikawa, Nagoya University, Japan

31. **Conceptual Design of TRR Medical Room for BNCT**
Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran

32. **Neutron Beam Based on the Nuclear Reactors: Using the Experiences for Accelerator-Based BNCT**
Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran

33. **^{124}SbBe Photo-Neutron Source for BNCT: Is It Possible?**
Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran

34. **Advances in the Autoradiography Technique for Boron-10 Quantification in Bone**
Lucas Provenzano, National Atomic Energy Commission (CNEA), Argentina

35. **3D SPECT reconstructed image from prompt gamma ray in BNCT for a heterogeneous human phantom: A Monte Carlo simulation study**
Chunhui Gong, Nanjing University of Aeronautics and Astronautics, China

Tuesday, October 4, 2016
Donald W. Reynolds Alumni & Visitor Center

8:00 am - 6:00 pm
Exhibits

BREAKOUT SESSION 1
8:30 am - 9:45 am

Breakout Session 1: Group 1, Physics ..... Columns A/B

8:30 am - 8:45 am
High-Power Liquid-Lithium Target Neutron Source Operation Experience and Gamma Radiation Characterization
Shlomi Halfon, Soreq NRC, Israel

8:50 am - 9:05 am
Design and Optimization of the Beam Shaping Assembly of a Deuterium-Deuterium Neutron Generator-Based BNCT System
Ming-Jung Hsieh, Purdue University, Indiana, USA

9:10 am - 9:25 am
Status of Accelerator Based BNCT Neutron Irradiation System using ^{7}Li(p,n)^{7}Be Near Threshold Reactions for Liquid Lithium Target
Tooru Kobayashi, K2BNCT Science & Engineering Laboratory Co. Ltd, Japan

9:30 am - 9:45 am
Thermal neutron source based on medical electron Linac
Valeria Monti, Department of Physics, University of Torino, Italy

Breakout Session 1: Group 2, Biology ..... Columns C

8:30 am - 8:45 am
Evaluation of relationship between uptake of L-BPA in Clear Cell Sarcoma Cell Line and L-type amino acid transporter 1
Tooru Andoh, Kobe Gakuin University, Japan

8:50 am - 9:05 am
Biokinetic of BPA for liver malignancies: Preclinical, clinical and extrapolation studies
Matthias Blaickner, Health and Environment Department, AIT Austrian Institute of Technology GmbH, Austria

9:10 am - 9:25 am
Electroporation enhances tumor control induced by GB-10-BNCT in the hamster cheek pouch oral cancer model
Marcela Garabalino, Atomic Energy Commission of Argentina (CNEA), Argentina

9:30 am - 9:45 am
Therapeutic efficacy of Boron Neutron Capture Synovectomy (BNCS) mediated by GB-10 or BPA in a model of antigen-induced arthritis in rabbits: low dose radiobiological studies at RA-1 Nuclear Reactor
Veronica A. Trivillin, Atomic Energy Commission of Argentina (CNEA), Argentina

Breakout Session 1: Group 3, Chemistry.....Columns D/E

8:30 am - 8:45 am
A theranostic approach using Gd/B probes combined with antitumour agents to improve Boron Neutron Capture Therapy efficacy
Simonetta Geninatti Crich, University of Torino, Department of Molecular Biotechnology and Health Sciences, Italy

8:50 am - 9:05 am
Carborane and metallacarborane inhibitors of Carbonic Anhydrase IX, compounds with possible double action
Bohumir Grüner, Institute of Inorganic Chemistry, AS CR, v.v.i., Czech Republic

9:10 am - 9:25 am
Development of New Generation Drug Delivery System for Boron Neutron Capture Therapy
Ming-Hua Hsu, Nuclear Science and Technology Development Center/National Tsing Hua University, China

9:45 am - 10:15 am
Break

PLENARY SESSION 4
10:15 am - 11:50 am | Columns Ballroom

10:15 am - 10:35 am
Re-start of Clinical and Pre-Clinical BNCT Activities at the Argentine RA-6 Nuclear Reactor
Gustavo Santa Cruz, Atomic Energy Commission of Argentina (CNEA) and National Research Council, Argentina

10:40 am - 11:00 am
Patient Activation Survey for BNCT Clinical Trials at THOR
Chun-Kai Huang, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan

11:05 am - 11:25 am
Nanostructured Boron Compounds: Applications in Cancer Therapy
Narayan Hosmane, Northern Illinois University, USA

11:30 am - 11:50 am
BNCT studies in the hamster cheek pouch oral cancer model employing different treatment strategies and the boron carriers BPA, GB-10 or MAC-TAC liposomes
Mandy Schwint, Atomic Energy Commission of Argentina (CNEA) and National Research Council, Argentina

11:50 am - 2:00 pm
Lunch and Exhibits

PLENARY SESSION 5
2:00 pm - 3:10 pm | Columns Ballroom

2:00 pm - 2:20 pm
Characterization of a CdZnTe detector prototype for Boron imaging by SPECT: simulations and measurements in a neutron field
Setareh Fatemi, University of Pavia & National Institute of Nuclear Physics (INFN), Italy

2:25 pm - 2:45 pm
Synthesis of Cobalt and Iron Bis(dicarbollide) Derivatives for Potential BNCT Application
Vladimir Bregadze, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Russia

2:50 pm - 3:10 pm
An Effective Therapeutic Method for Treating Multifocal Liver Tumor: Boric Acid-mediated BNCT in VX2 Liver Tumor-bearing Rabbit Model
Fong-In Chou, Nuclear Science and Technology Development Center, National Tsing Hua University, Taiwan

POSTER SESSION 2
3:15 pm - 4:15 pm | Great Room

1. **The Investigation for Optimization of Melanoma BNCT Models in Mice**
   Shoji Imamichi, Division of Chemotherapy and Clinical Research, National Cancer Center Research Institute, Japan
2. **The DNA Double-Strand Breaks Damage in CHO Cells Induced by the Fractionated Neutron Irradiation**
   Yuko Kinashi, Research Reactor Institute, Kyoto University, Japan
3. **Gadolinium Neutron Capture Therapy for Brain Tumor Therapy: A Preliminary Evaluation**
   Wei-Neng Liao, Institute of Biomedical Engineering & Nanomedicine, National Health Research Institutes, Taiwan
4. **Effect of Oxygen Pressure During Incubation with a ^{10}B-Carrier on ^{10}B Uptake Capacity of Cultured *p53 Wild-Type* and *Mutated* Tumor Cells With Reference to Dependency on *p53 Status* of Tumor Cells and of ^{10}B-carriers**
   Shin-ichiro Masunaga, Research Reactor Institute, Kyoto University, Japan
5. **Topical application of Histamine Gel Would Protect Oral Precancerous Tissue from BNCT Induced Mucositis, but Would Affect Therapeutic Effect on Tumors: Preliminary Studies in an Oral Cancer Model**
   Andrea Monti Hughes, National Atomic Energy Commission (CNEA), Argentina
6. **Translational BNCT Studies in the Hamster Cheek Pouch Model of Oral Cancer at the New Configuration of the RA-6 Nuclear Reactor**
   Andrea Monti Hughes, National Atomic Energy Commission (CNEA), Argentina

7. **Development of Dual Formulations as Boron Neutron Capture Therapy Agents**
   Hong Chuang, Department of Chemistry, National Tsing Hua University, Taiwan
8. **Microdistribution and Excretion Pathways of Boron Neutron Capture Therapy Agents Delivered by rationally Designed Liposomes**
   Thomas Everett, International Institute of Nano & Molecular Medicine, University of Missouri, USA
9. **Detection of Boron-Pharmaceuticals in Live Cancer Cells Using Fluorescent Boron-Sensor**
   Yoshihide Hattori, Research Center of BNCT, Osaka Prefecture University, Japan
10. **Preparation and Evaluation of Complexes of Boric Acid and Hydrogen Fluoride for Boron Neutron Capture Therapy**
    Fong-In Chou, Nuclear Science and Technology Development Center, National Tsing Hua University, Taiwan
11. **Estimation of Radioactivation of Dental materials and Neutron Loss by Dental Materials, and the Measure for Those Problems**
    Toshiyuki Kubota, Kbota Dental Clinic, Japan
12. **Experimental Study of Uptake the Boron Compound in Glioma Stem Cell**
    Tadashi Kurita, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Japan
13. **Effects of the Fast-Neutron-Rate in a Neutron Beam and the Boron-Density in a Phantom on the RBE Dose Calculations for the Accelerator-Based BNCT**
    Takuya Oie, Graduate School of Engineering, Hokkaido University, Japan
14. **In-phantom Gel Dosimetry in TRR BNCT Beam Line**
    Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran
15. **The Effect of the Moderator: Reflector Geometry of BSA on the Skin Dose During BNCT of Brain Tumors**
    Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran
16. **Investigation on the BNCT for Liver at TRR**
    Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran
17. **A Comparison of Proton Therapy and BNCT at TRR in Treatment of Brain Tumors Using the High-Resolution Voxel-Based Zubal Head Phantom**
    Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran
18. **A New Approach to use D-T Neutron Generator for BNCT**
    Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran
19. **Modern Arak Heavy Water Research Reactor for BNCT**
    Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran
20. **Dosimetric Impact Due to Intratreatment Positioning Error in Boron Neutron Capture Therapy for the High-grade Glioma**
    Takahiro Kato, Southern Tohoku BNCT Research Center, Japan

21. **Potential of NIPAM Polymer Gel in 3D Mapping of Dose Distribution in Shallow Brain Tumors Treated Using BNCT**
Azim Khajeali, Faculty of Medicine, Department of Medical Physics, Tabriz University of Medical Sciences, Iran

22. **Development of the Accelerator Based Boron Neutron Capture Therapy System for Cancer Treatment within 1 Hour Therapeutic Time**
Dong-su Kim, DAWONSYS, Republic of Korea

23. **Design of a Beam Shaping Assembly for the Nagoya University BNCT Engineering Study System**
Yoshiaki Kiyanagi, Nagoya University, Japan

24. **An Approach to be a General Radiation Therapy for BNCT**
Tooru Kobayashi, K2BNCT Science & Engineering Laboratory Co. Ltd, Japan

25. **A New Production Method for Patient Fixing Implement by Combination with a Three-Dimensional Printing Technique and Treatment Planning System**
Hiroaki Kumada, University of Tsukuba, Japan

26. **Assessment of the Reaction and Additional Dose from the Spine-Fixation Screws In Boron Neutron Capture Therapy**
CANCELLED
Yu-Cheng Kuo, Department of Radiation Oncology, Show-Chwan Memorial Hospital, Changhua County, Taiwan

27. **Induced Radioactivity and Residual Dose Rates in a Boron Neutron Capture Therapy Facility Based on Be(p,xn) Reaction with 30 MeV Protons**
Bo-Lun Lai, National Tsing Hua University, Taiwan

28. **A comparison of dose distributions in GTV between BNCT alone and combined BNCT-IMRT Treatment Planning for Head and Neck Cancer**
Jia-Cheng Lee, Department Oncology, Taipei Veterans General Hospital, Taiwan

29. **A bi-tapered and air-gapped beam shaping assembly used for AB-BNCT**
Pei-Yi Lee, Neuboron Medtech Ltd., China

30. **Extension Collimator Designed and Used for BNCT Clinical Trial at THOR**
Hong-Ming Liu, National Tsing Hua University, Taiwan

31. **Using Lithium-6 Filter for Study of Dose Distribution with Maximum and Minimum Displacement of Prostate Inside the Body in BNCT Method**
Dawod Mirzaee, Department of Physics, Faculty of Sciences, Ferdowsi University of Mashhad, Iran

32. **Development of Treatment Planning System for In-Hospital BNCT System**
Tetsuya Mukawa, Sumitomo Heavy Industries, Ltd., Japan

33. **Estimation for Exposure Dose to Medical Workers in an Accelerator-Based BNCT system with a Li target**
Masayoshi Munechika, Tokyo Metropolitan University, Japan

34. **Monte Carlo Simulation of Depth-Dose Distribution in Brain Model for Boron Neutron Capture Therapy**
Rachid Khelifi, University of Blida, Algeria

35. **Development of a Moderator-Based Spherical Neutron Detector for BNCT**
Takemi Nakamura, Japan Atomic Energy Agency, Japan

BREAKOUT SESSION 2
4:30 pm - 5:45 pm

Breakout Session 2: Group 1, Physics ..... Columns A/B

4:30 pm - 4:45 pm
Methodology for Dosimetric Characterization of the Neutron Therapeutics Accelerator-Based BNCT System
Iiro Auterinen, Neutron Therapeutics, Finland

4:50 pm - 5:05 pm
Comparison between TLD-700 and TLD-100 reliability for measuring both gamma dose and thermal-neutron fluence in radiation fields for NCT
Grazia Gambarini, Department of Physics, University of Milan, Italy

5:10 pm - 5:25 pm
Computational Dosimetry Comparison between External Ion Beam Therapy and BNCT
Ming-Chen Hsiao, Neuboron Medtech Ltd., China

Breakout Session 2: Group 2, Biology ..... Columns C

4:30 pm - 4:45 pm
An early inflammatory and immune cascade activation after BNCR in human cancer cells
Mitsuko Masutani, Nagasaki University, Japan

4:50 pm - 5:05 pm
CBE factors for boron compounds to the tumor varies depending on their ^{10}B levels – radiobiological consideration about its significance –
Koji Ono, Kyoto University Research Reactor Institute, Japan

5:10 pm - 5:25 pm
Biodistribution and convection-enhanced delivery of the boronated porphyrin in the F98 intracerebral rat glioma model
Hiroyuki Shiba, Department of Neurosurgery, Osaka Medical College, Japan

Breakout Session 2: Group 3, Chemistry ..... Columns D/E

44:30 pm - 4:45 pm
Approaches to the Synthesis of Boronic Acid-Derived Sugars
Daniela Imperio, Department of Pharmaceutical Sciences, University of Eastern Piedmont, Italy

4:50 pm - 5:05 pm
Hypoxia Targeted Boron Delivery Agent for BNCT Treatment of Brain Tumor
David (Y.W.) Lee, Harvard Medical School/McLean Hospital, Massachusetts, USA

5:10 pm - 5:25 pm

Boramino Acid: A New Theranostic Platform Serves Imaging Guided Boron Neutron Capture Therapy

CANCELLED

Zhibo Liu, National Institutes of Health, Maryland, USA

Breakout Session 2: Group 4, Clinical ..... T. O. Wright Room

4:30 pm - 4:45 pm

Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the assessment of radiation treatment in patients with re-recurrence head and neck squamous cell carcinoma

Teruhito Aihara, Proton Medical Research Centre, University of Tsukuba, Japan

4:50 pm - 5:05 pm

Personalized BNCT?

Allah Detta, University Hospital Birmingham, United Kingdom

5:10 pm - 5:25 pm

A case of boron neutron capture therapy for recurrent oral cavity cancer

Yuta Sekino, Proton Medical Research Centre, University of Tsukuba, Japan

5:30 pm - 5:45 pm

Boron neutron capture therapy (BNCT) combined with image-guided intensity modulated radiotherapy (IG-IMRT) for locally recurrent head and neck cancer: a preliminary report

Ling-Wei Wang, Taipei Veterans General Hospital, Taiwan

Wednesday, October 5, 2016

Donald W. Reynolds Alumni & Visitor Center

8:00 am - 4:00 pm
Exhibits

PLENARY SESSION 6

8:30 am - 10:05 am | Columns Ballroom

8:30 am - 8:50 am
The first NCT clinical trial of skin melanoma at In-Hospital Neutron Irradiator
Zizhu Zhang, China Nuclear Industry Beijing 401 Hospital & Beijing Capture Technology Co. Ltd., China

8:55 am - 9:15 am
Items Layout of Nuclear Medical Ship for Neutron Capture Therapy (NCT) Clinical Studies and Trials
Guotu Ke, China Institute of Atomic Energy (CIAE), China

9:20 am - 9:40 am
BNCT and some of its returning misconceptions
Detlef Gabel, Department of Life Sciences and Chemistry, Jacobs University, Germany

9:45 am - 10:05 am
Targeting the Glioma Hypoxic Tumor Microenvironment with a Novel Boron Neutron Capture Therapy Agent
Micah Luderer, Washington University in St. Louis School of Medicine, Missouri, USA

10:10 am - 10:50 am
General Assembly Meeting

POSTER SESSION 3

10:55 am - 11:55 am | Great Room

1. **Preclinical Studies to Optimize the Application of Boron Neutron Capture Therapy (BNCT) for Treatment the Superficial Cancer**
   Susana Isabel Nievas, Department of Boron, Constituyentes Atomic Center. National Atomic Energy Commission (CNEA), Argentina
2. **Pilot studies to evaluate the effectiveness of high LET particle irradiation in damaging neurotoxic protein aggregates**
   Ian Postuma, University of Pavia, Department of Physics and National Institute of Nuclear Physics (INFN), Italy
3. **Evaluation of BSH containing Kojic acid (KA-BSH) as a novel agent for boron neutron capture therapy**
   Koji Takeuchi, Department of Neurosurgery, Osaka Medical College, Japan
4. **Abscopal Effect of BNCT**
   Veronica A. Trivillin, National Atomic Energy Commission (CNEA), Argentina

5. **L-Phenylalanine preloading reduces the $^{10}B(n,\alpha)^{7}Li$ dose to the normal brain by inhibiting the uptake of L-BPA**
   Tsubasa Watanabe, Kyoto University Research Reactor Institute, Japan

6. **Property and in vitro study of a liposome modified boron lipid for combination therapy**
   Makoto Shirakawa, University of Fukuyama, Department of Pharmaceutical Sciences, Japan

7. **Development of *closo*-Dodecaborate-Serum Albumin Conjugates via Ruthenium-Photocatalyzed Tyrosine Modification for Neutron Capture Therapy**
   Satomu Ishii, Tokyo Institute of Technology, Japan

8. **Synthesis of water-dispersible boron nitride nanosheets for boron neutron capture therapy**
   Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran

9. **Synthesis of Fluorescein-Tagged and Water-Soluble Carborane-Appended Compounds**
   Lucas Kuzmanic, Northern Illinois University, USA

10. **BNCT Antitumor Effect of Boron Nitride Nanotubes**
    Hiroyuki Nakamura, Chemistry and Life Science (CLS), Institute of Innovative Research, Tokyo Institute of Technology, Japan

11. **Neutron penetration profile in tissue like phantoms with different neutron energies**
    Rainer Tietze, ENT-Department, Else Kröner-Fresenius-Stiftung Professorship, Section for Experimental Oncology and Nanomedicine (SEON), University Hospital Erlangen, Germany

12. **How Boron Neutron Capture Therapy and other Innovative Therapies can be Game Changers in Palliative Care**
    Daniel Quah, National Cancer Center, Singapore

13. **Boron neutron capture therapy for multiple liver metastases: A case report**
    Minoru Suzuki, Research Reactor Institute, Kyoto University, Japan

14. **A study for the improvement of a thermal neutron irradiation equipment for BNCT researchers at Kyoto University Reactor – An installation of beam monitor system**
    Keita Okazaki, Kyoto University, Japan

15. **Conceptual design of an accelerator based neutron source for BNCT and other applications**
    Ignacio Porras, University of Granada, Spain

16. **Tailoring of an epithermal neutron beam for the RFQ-based facility of INFN**
    Ian Postuma, University of Pavia, Department of Physics and National Institute of Nuclear Physics (INFN), Italy

17. **A new model for the determination of the biological dose in BNCT: weighted kerma factors and the LQ model**
    Javier Praena, University of Granada, Spain

18. Thermal scattering libraries and their impact on neutron transport for BNCT dosimetry: experimental assessments
Silva Bortolussi, University of Pavia & National Institute of Nuclear Physics (INFN), Italy

19. Comparative study of boron uptake by different tissues, with main focus on calcified tissues, administered as boric acid and BPA in high doses
Agustina Portu, National Commission of Atomic Energy (CNEA), Argentina

20. Evaporation in Tissue Sections used for Neutron Autoradiography in BNCT
Agustina Portu, National Commission of Atomic Energy (CNEA), Argentina

21. Gadolinium effect estimation of GAGG for BNCT-SPECT
Nobuhide Saraue, Divison of Sustainable Energy and Environmental Engineering, Graduate School of Engineering, Osaka University, Japan

22. Feasibility study for estimation of hydrogen density distribution using MR imaging for pleural mesothelioma BNCT
Hiroyuki Sato, Department of Radiology, Tottori University Hospital, Japan

23. Development of neutron collimator for the new wide dynamic range neutron spectrometer for BNCT
Shingo Tamaki, Osaka University, Japan

24. Investigation of beam component monitor for BNCT using gel detector
Kenichi Tanaka, Hiroshima University, Japan

25. Study on irradiation field monitor for BNCT using multi imaging plate system
Kenichi Tanaka, Hiroshima University, Japan

26. Proton beam of 5 mA in the Tandem Accelerator with Vacuum Insulation
Sergey Taskaev, Budker Institute of Nuclear Physics, Russia

27. Beam Shaping Assembly for BINP Neutron Source
Sergey Taskaev, Budker Institute of Nuclear Physics, Russia

28. Lithium Neutron Producing Target
Sergey Taskaev, Budker Institute of Nuclear Physics, Russia

29. The Effect of Non-uniform Boron Distribution on Treatment Planning Dose Calculation
Yi-Chiao Teng, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan

30. Thermal-hydralic Design and Analysis of A New Cone Lithium Target for BNCT
Jianfei Tong, Institute of High Energy Physics (IHEP), Chinese Academy of Sciences (CAS), China

31. Thermal Neutron Fluence and Gamma-ray Dose QA Using CaF_2:Mn TLD for BNCT Beam at THOR
Chun-Kai Huang, Department of Engineering and System Science, National Tsing Hua University, Taiwan

32. Experimental Estimation of Neutron Yield from ^{7}Li(p,n) Reaction for Source Term Estimation System for BNCT
Keita Uehara, Graduate School of Engineering Osaka University, Japan

33. **Investigation of Methods of Establishing Equivalent Surface Source for BNCT Treatment Planning Calculation**
Zhen-Fan You, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan

34. **The Boron Neutron Capture Therapy (BNCT) Program at the University of Missouri International Institute of Nano & Molecular Medicine (I^2NM^2)**
Alice Raphael Karikachery, International Institute of Nano & Molecular Medicine, University of Missouri, USA

11:55 am - 12:55 pm
Lunch

PLENARY SESSION 7
1:00 pm - 2:35 pm | Columns Ballroom

1:00 pm - 1:20 pm
BNCT Laboratory in BINP
Sergey Taskaev, Budker Institute of Nuclear Physics, Russia

1:25 pm - 1:45 pm
Present status of BNCT System using 30 MeV Cyclotron
Toshinori Mitsumoto, Sumitomo Heavy Industries, Ltd., Japan

1:50 pm - 2:10 pm
BNCT for Malignant Brain Tumors, from Reactor to Accelerator
Shin-Ichi Miyatake, Osaka Medical College, Japan

2:15 pm - 2:35 pm
Preliminary study on feasibility of boron neutron capture therapy in patients of diffuse intrinsic pontine glioma without craniotomy
Yuan-Hung Wu, Taipei Veterans General Hospital, Taiwan

2:35 pm - 3:00 pm
Break

BREAKOUT SESSION 3
3:00 pm - 4:15 pm

Breakout Session 3, Group 1, Physics ..... Columns A/B
3:00 pm - 3:15 pm
Clinical application of the photon iso-effective dose concept in BNCT from dose-response assessments in an in-vivo oral cancer model
Sara González, National Commission of Atomic Energy (CNEA), Argentina

3:20 pm - 3:35 pm
The prospective of BNCT Project at Tehran Research Reactor
Yaser Kasesaz, Nuclear Science and Technology Research Institute (NSTRI), Iran

3:40 pm - 3:55 pm
Computational analysis of the feasibility of treating head and neck cancer with BNCT at the RA-6 Reactor
Lucas Provenzano, National Commission of Atomic Energy (CNEA), Argentina

4:00 pm - 4:15 pm
Boron Neutron Capture Therapy for Extensive Scalp Lesions: Treatment Planning Study
Takushi Takata, Kyoto University Research Reactor Institute, Japan

Breakout Session 3, Group 2, Biology ..... Columns C

3:00 pm - 3:15 pm
Application of carbon nanohorn containing boron to BNCT
Kei Nakai, Ibaraki Prefectural University Of Health Sciences, Japan

3:20 pm - 3:35 pm
Neutron irradiation of human glioma cultured cells using accelerator based neutron source
Alexander Zaboronok, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Japan

3:40 pm - 3:55 pm
Boron delivery system using boronated polyethylene-glycol binding BSA for boron neutron capture therapy *in vitro*
Hironobu Yanagie, Meiji Pharmaceutical University, Japan

4:00 pm - 4:15 pm
Development of a real-time prompt gamma-ray imaging system using GAGG:Ce or SrI_2:Eu scintillator array for BNCT
Hiroki Tanaka, Kyoto University Research Reactor Institute, Japan

Breakout Session 3, Group 3, Chemistry .....Columns D/E

3:00 pm - 3:15 pm
Novel ROS-scavenging, Boron-Cluster-containing Nanoparticles for Highly Effective BNCT with Low Adverse Effects
Zhenyu Gao, Graduate School of Pure and Applied Sciences, University of Tsukuba, Japan

3:20 pm - 3:35 pm
Development of a 3D cell culture model for depth dependent BNCT efficacy evaluations of boron containing magnetic nanoparticles
Harald Unterweger, University Hospital Erlangen, Section of Experimental Oncology and Nanomedicine (SEON), Germany

3:40 pm - 3:55 pm
PGNAA facility for BNCT at RA-3: numerical approach towards beam requirements
Matias Valero, Favaloro University, Argentina

5:45 pm – 6:00 pm

Group Photo

Please be available Wednesday at 5:45 pm on the plaza outside the Alumni Center, on the east side.

Banquet & Reception

6:00 pm - 9:00 pm | Columns Ballroom

Thursday, October 6, 2016

Donald W. Reynolds Alumni & Visitor Center

8:30 am - 1:30 pm
Exhibits

8:30 am - 9:00 am
Executive Board Meeting

BREAKOUT SESSION 4

9:00 am - 10:15 am

Session 4, Group 1, Physics ..... Columns A/B

9:00 am - 9:15 am
The Neutron Therapeutics Solid Lithium Neutron Target For Accelerator-Based BNCT
Bill Park, Neutron Therapeutics, Finland

9:20 am - 9:35 am
A Multi-beam DD Neutron Generator with an Internal Cylindrical Moderator: Its First Operation and Possible Use for Neutron Capture Therapy
Melvin Piestrup, Adelphi Technology Inc., California, USA

9:40 am - 9:55 am
Gamma-ray Production from a Proton-Lithium Neutron Source and Its Impact on Boron Neutron Capture Therapy
Tatsuhiro Saito, Tokyo Institute of Technology, Japan

10:00 am - 10:15 am
Optimum Neutron Energy Spectrum as the basis of Tunable Moderators for Next Generation Accelerators of Boron Neutron Capture Therapy (BNCT)
Ryoichi Seki, Research Center for Nuclear Physics, Osaka University, Japan

Session 4, Group 2, Physics ..... Columns C

9:00 am - 9:15 am
Enhancing Resolution in Neutron Autoradiography of Tissue Samples by UV-C Sensitization
Agustina Portu, National Commission of Atomic Energy (CNEA), Argentina

9:20 am - 9:35 am
Development of remote-changeable Bonner-sphere spectrometer for QA/QC in BNCT
Yoshinori Sakurai, Kyoto University Research Reactor Institute, Japan

9:40 am - 9:55 am
Computational Dosimetry by Monte Carlo Calculation for Several BNCT Facilities with New Treatment Planning System "Tsukuba-Plan"
Kenta Takada, Faculty of Medicine, University of Tsukuba, Japan

10:00 am - 10:15 am
Study of Polymer Gel Dosimeter Response in Neutron Irradiation Fields
Ryohei Uchida, Kyoto University, Japan

Session 4, Group 3, Physics .....Columns D/E

9:00 am - 9:15 am
Compact Accelerator-Driven BNCT System Used Sealed Lithium Target
Kazuki Tsuchida, Nagoya University, Japan

9:20 am - 9:35 am
Characterization of the neutron beams at the IHNI-1 for BNCT
Zizhu Zhang, China Nuclear Industry Beijing 401 Hospital & Beijing Capture Technology Co. Ltd., China

9:40 am - 9:55 am
Development of the Neutron Therapeutics Accelerator-Based BNCT System
Noah Smick, Neutron Therapeutics, Finland

10:00 am - 10:15 am
Accelerator Based Neutron Capture Therapies in France
Daniel Santos, LPSC, Grenoble-Alpes University, CNRS-IN2P3, France

10:15 am - 10:40 am
Break

PLENARY SESSION 8
10:45 am - 12:20 pm | Columns Ballroom

10:45 am - 11:05 am
Feasibility Study of Boron Neutron Capture Therapy for the Treatment of Osteosarcoma
Silva Bortolussi, University of Pavia, National Institute of Nuclear Physics (INFN), Italy

11:10 am - 11:30 am
Towards ^{10}B neutron capture reaction mapping in a patient with photon-counting SPECT systems
Hanna Koivunoro, Neutron Therapeutics, Finland

11:35 am - 11:55 am
Clinical results of reactor-based BNCT using BPA for the patients with recurrent malignant glioma
Shin-Ichi Miyatake, Koji Takeuchi, **Hiroyuki Shiba**, Department of Neurosurgery, Osaka Medical College, Japan

12:00 pm - 12:20 pm
Development of Linac-based neutron source for BNCT (i-BNCT project)
Akira Matsumura, University of Tsukuba, Japan

12:20 pm - 1:15 pm
Lunch

1:15 pm - 9:00 pm
Pre-paid Excursion
Lake of the Ozarks

Friday, October 7, 2016
Hampton Inn & Suites, Columbia

PLENARY SESSION 9
9:00 am - 10:35 am | University Room

9:00 am - 9:20 am
Time course changes in ^{18}F-BPA uptake dynamics by PET scan
Hiroshi Igaki, National Cancer Center Hospital, Japan

9:25 am - 9:45 am
Cerebrospinal fluid (CSF) dissemination of malignant gliomas following treatment with boron neutron capture therapy (BNCT)
Natsuko Kondo, Kyoto University Research Rector Institute, Japan

9:50 am - 10:10 am
Case experience of boron neutron capture therapy for radiation-induced cranial osteosarcoma
Hiroyuki Shiba, Department of Neurosurgery, Osaka Medical College, Japan

10:15 am - 10:35 am
Boron neutron capture therapy in skull base high-grade meningioma
Koji Takeuchi, Department of Neurosurgery, Osaka Medical College, Japan

10:35 am - 11:00 am
Break

11:00 am - 12:00 pm
Closing Session

12:30 pm - 1:30 pm
Executive Board Meeting & Lunch

PLENARY SESSIONS

Requalification and Experimental Validation of the Epithermal Neutron Beam Facility for Radiotherapy Research at Washington State University

David W. Nigg[1], Kaitlyn R. Restis[2], Sara M. Dickens[2], C. Corey Hines[2], Mathew D. King[2], Alexandra Bartkoski[2], and Donald E. Wall[2]

1. *Idaho National Laboratory, Idaho Falls, ID.*
2. *Washington State University, Pullman, WA*

Email: dwn@inl.gov

Approximately ten years ago the Idaho National Laboratory (INL) and Washington State University (WSU) completed the construction of a new epithermal-neutron beam for collaborative preclinical Neutron Capture Therapy (NCT) research at the WSU TRIGA™ research reactor facility. Since then the reactor core has been reconfigured to use Low-Enriched Uranium (LEU) fuel, and significant interest has emerged recently with respect to potential use of the facility for actual clinical (human) trials as well as for preclinical work. These developments have necessitated a complete experimental revalidation of the neutronic performance of the WSU epithermal neutron beamline. This paper summarizes the results of the physics requalification effort.

The WSU facility incorporates a high-efficiency neutron moderating and filtering material (FLUENTAL™) developed by the Technical Research Centre of Finland into the design. The WSU reactor core configuration at the time the original beamline was completed was based on a mix of High Enriched Uranium (HEU) fuel and LEU fuel elements. More recently the core was reconfigured to use only LEU fuel. Computational estimates indicated that this change likely would affect the beam intensity at the exit aperture somewhat, and that some slight changes in the neutron spectrum might possibly also be expected, largely due to increased neutron capture and inelastic scattering in the core because of the larger inventory of ^{238}U.

Neutronic computations for design and qualification of the original WSU beamline were performed using the MCNP and DORT radiation transport codes. Foil activation measurements based on protocols developed by the INL for neutron spectrum measurements at medical facilities elsewhere were made to characterize the free-beam neutron spectrum in the transverse plane at the exit of the conical bismuth collimator in the case of both the original beam and, in the present work, the new LEU based beam. Additional confirmatory measurements of the neutron beam intensity relative to that of the original beam were performed using cadmium-covered GE-Reuter-Stokes fission chambers placed within a bismuth shield located on the bottom inside surface of the collimator. Finally, measurements of the thermal and epithermal neutron flux profiles produced along the central axis in a standard cylindrical Lucite™ phantom with the beam incident on the end through a 10.16 cm (4”) diameter beam-shaping aperture composed of lithiated polyethylene were made for both beams.

Repeating the original beam qualification measurements for the new LEU-driven beam yielded a spectrum that was statistically indistinguishable from the original spectrum but with a slightly lower total intensity (1.49×10^9 n/cm^2-sec, or 89.8% of the original beam intensity). The WSU

facility is one of only three clinical-scale reactor-based epithermal-neutron sources for NCT research that have been constructed and operated U.S. and it is the only one currently in full operational status.

ACKNOWLEDGEMENT

This work was sponsored by the University of Missouri International Institute for Nano- and Molecular Medicine. The authors gratefully acknowledge the continuing support of Dr. M.F. Hawthorne, Director of the Institute, and Dr. Satish S. Jalisatgi, Deputy Director, and their staff.

New Gadolinium Agents for Binary Cancer Therapies

L.M. Rendina[1], *M. Busse*[1], *A.J. Hall*[1], *M. Kardashinsky*[1], *D.E. Morrison*[1], *M.S.A. Windsor*[1], *J.B. Aitken*[1,2,3], *M.D. de Jonge*[2], *H.H. Harris*[4]

[1] *School of Chemistry, The University of Sydney, Sydney NSW 2006, Australia.*
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In Gd neutron capture therapy (NCT), the Auger Coster-Krönig (ACK) electrons represent the main therapeutic entity derived from the thermal neutron capture reactions of the naturally-occurring and non-radioactive ^{157}Gd isotope, which possesses the highest neutron-capture cross-section of all stable nuclides (2.55 x 10^5 barns). In photon activation therapy (PAT), emission of ACK electrons from high-*Z* atoms can be achieved by means of X-ray photons due to the photoelectric effect and, unlike NCT, is independent of isotope. Thus, two related binary therapies for the treatment of aggressive and intractable cancers such as malignant gliomas can be considered for Gd. One critical aspect of both NCT and PAT is the development of tumour-selective agents containing Gd which can localize in high quantities (>100 ppm) near important sub-cellular components, e.g. DNA or mitochondria.

We have designed the first examples of Gd^{III} complexes which include an arylphosphonium functionality for tumour-cell targeting of mitochondria for NCT or PAT. We also have demonstrated their favourably low *in vitro* cytotoxicity in the absence of neutrons or X-ray photons, excellent *in vitro* tumour selectivity, preferential localization within the mitochondria of treated cells, and a capacity to deliver remarkably high levels of Gd into human glioblastoma multiforme (T98G) tumour cells (up to 10^{11} Gd atoms/cell, or *ca*. 3000 ppm) by means of both ICP-MS analysis and synchrotron XRF quantitation. Preliminary synchrotron PAT experiments, the first such experiments ever conducted in Australia, have been performed at the Australian Synchrotron. The key results of this work will be presented.

Molecular Targeting of Boron Delivery Agents for Neutron Capture Therapy of Brain Tumors in the Genomic Era

Rolf F. Barth[1]

[1]*Department of Pathology, The Ohio State University, Columbus, OH 43210 U.S.A.*

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Three specific molecular targets will be discussed. The *first* is the Epidermal Growth Factor Receptor (EGFR) and its mutant isoform EGFRvIII using boronated monoclonal antibodies (MoAbs) as the targeting moieties. The *second* is the vascular endothelial growth factor receptor (VEGFR), using a human recombinant $VEGF_{121}$ construct as a fusion protein with a novel cysteine-containing peptide fusion tag linked to a heavily boronated macromolecule. The *third* is thymidine kinase 1 (TK1), which is overexpressed in a wide variety of malignant tumors, using a group of carboranyl thymidine analogues (CTAs) as the delivery agents.

Turning *first* to EGFR, our studies initially focused on two mouse anti-human MoAbs as potential targeting agents: cetuximab (C225 or, as it is now marketed, Erbitux®), which was directed against wildtype EGFR; and the other, L8A4, which was directed against EGFRvIII. Initially, a procedure was developed to heavily boronate these MoAbs using precision macromolecules, PAMAM dendrimers (D), as the boron carrier (BD). These were linked to the MoAbs using two heterobifunctional reagents, KMUH and SPDP. The resulting bioconjugates, designated BD-C225 and BD-L8A4, then were evaluated *in vitro*, and then *in vivo* with $F98_{EGFR}$ and $F98_{EGFRvIII}$ gliomas, which had been genetically engineered to express human EGFR and EGFRvIII, respectively. For *in vivo* biodistribution studies the bioconjugates were administered intracerebrally (i.c.) to glioma bearing Fischer rats by means of convection enhanced delivery (CED) in order to maximize tumor uptake and minimize uptake by extracranial organs. *In vivo* BNCT studies were carried out at the MIT Research Reactor (MITRR). In animals bearing composite brain tumors ($F98_{EGFR}$/$F98_{EGFRvIII}$) the longest mean survival time (MST) was observed in rats that had received both bioconjugates (MST 55 ±5 d, range 37-87 d) compared to those animals that received one or the other bioconjugate. These results demonstrated that both tumor cell populations had to be targeted, and that even then, there were no cures. The best therapeutic results were obtained using the bioconjugates in combination with i.v. administration of BPA, suggesting that molecularly and non-molecularly targeted agents should be used together.

The *second* approach was to target VEGFR using $VEGF_{121}$ as the targeting moiety, which was linked to heavily boronated PAMAM dendrimers via the heterobifunctional reagent SPDP, labeled with a near-IR dye, Cy5, as a tracer for imaging studies. Specific targeting of the bioconjugate designated VEGF- BDCy5 was demonstrated *in vitro* with the porcine endothelial cell line 293/KDR, and *in vivo* by means of IR-fluorescent imaging of tumor vasculature of subcutaneous 4T1 breast carcinomas in BALB/c mice. However, no *in vivo* BNCT studies were carried out to evaluate therapeutic efficacy.

The *third* approach focused on using a CTA designated N5-2OH in Fischer rats bearing either

F98 or RG2 gliomas. Initially carboranyl nucleosides had been synthesized by Soloway and his research team and subsequently this work was extended by Tjarks and his research group to produce a library of CTAs. N5-2OH was administered i.c. by means of CED, and BNCT was carried out at the MITRR. RG2 glioma bearing rats had a significant increase in MST (45.6 d) compared to irradiated controls (28.1 d). Therapeutic efficacy was further increased by combining N5-2OH with i.v. BPA (MST of 52.9 d vs
36.7 d for BPA alone). Unexpectedly, there was no such demonstration of a significant therapeutic gain in F98 glioma bearing rats that received N5-2OH alone or with BPA (MST 37.9 d vs 36.7 d), despite the fact that these tumors also strongly expressed TK1. The advantages and disadvantages of molecular targeting strategies will be discussed based on the three examples that have been presented.

Worldwide Status of Accelerator-Based BNCT

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There is an international consensus that Accelerator-Based BNCT (AB-BNCT) may change the prospects of BNCT due mainly to the possibility of in-hospital siting in contrast to reactor-based facilities. Hence, there is a quest worldwide for finding the "best" technological solution for such a facility. Decision criteria may be: simplicity, safety and lowest possible cost in order to promote widest possible dissemination.
There are several high intensity accelerator-based facilities being constructed and tested worldwide. Progress since ICNCT-16 will be assessed. The different options will be compared according to the nuclear reaction employed, beam energy and current, resulting primary neutron spectra features, target design and complexity, resulting epithermal neutron beam characteristics, type of machine, cost, etc. Merits and demerits will be discussed.
In particular, the progress of the Argentine Electrostatic Quadrupole accelerator is described. A less-than-final-scale prototype is ready which has been shown to transmit proton beams of about 10 mA. Beam diagnostics through fluorescence induced in the residual gas of the accelerator tube and emittance determinations will be presented. Larger machines are also being built.
Our attention is preferentially focused on deuteron-induced reactions and in particular in $^{9}Be(d,n)^{10}B$, since they allow for the smallest possible machines. Its suitability for AB-BNCT will be briefly mentioned. Progress in Be-based neutron production targets will also be briefly described.
A new accelerator development laboratory and future treatment facility is under construction in Argentina and its current status will be shown.

Extra-corporal BNCT for liver malignancies: Lessons learnt from 'Liver Purge'

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The first clinical BNCT application of an explanted cancerous liver in Pavia, Italy, using a TRIGA reactor, was a scientific as well as clinical sensation. Ever since the question has remained of how this treatment procedure can be optimized. The purpose of the research project "Liver purge" was to provide the biomedical and technical basis for advanced, future clinical trials of an extra-corporal liver BNCT.

On the dosimetric side the complex neutron-gamma field of the TRIGA research reactor in Mainz was described by means of Monte Carlo simulations (MCNP and FLUKA) and measurements. Criticality calculations were used to simulate the radiation field of the entire reactor and validated with alanine dosimeters, gold foils and an online pin-diode detector. Thus, it could be demonstrated that doses of 30-50 Gy in a tumor can be achieved with an irradiation time no more than 10 minutes, depending on the tumor to liver ratio of ^{10}B. Regarding tracers' kinetics it was shown by means of preclinical studies, extrapolated to human as well as clinical data, that [^{18}F]FBPA predicts L-BPA concentration in a hepatocellular mouse tumor model. Furthermore [^{18}F]FBPA – PET/MR scans were conducted in a rat model and demonstrated the advantages of this multimodal imaging method when a MRI contrast medium was applied. Preloading with L-BPA, L-DOPA or L-tyrosine did not increase BPA uptake in hepatocellular tumors. Extrapolation studies yielded interspecies similarities for the ^{10}B bio-distribution in liver and the tumor to blood ratio and underestimations of the boron concentration in tumor for mice and subsequently the tumor/liver ratio. All available data indicate that the tumor to liver ratio is steadily increasing and reaches saturation approximately 2 hours after start of administration. Therefore the optimal time point for transplantation and irradiation was calculated to be 120 minutes post injection.

Finally, assuming a maximal tolerable dose to healthy liver tissue of ~15 Gy as well as 10ppm in non-cancerous tissue and applying the developed computational dose calculation it follows that the liver to tumor ratio of BPA measured in the scope of this project (2.3 – 3.5) results in tumor doses < 30 Gy, which is too low from a therapeutic point of view. A ratio > 5 on the other hand ensures a minimum dose to tumor of > 30 Gy as well as a difference to the maximum dose in healthy tissue of > 20 Gy. Therefore this project concludes that for extra-corporal liver BNCT ^{10}B carriers with a higher tumor to healthy tissue ratio should be investigated.

Production of ^{10}B-enriched materials at the International Institute of Nano and Molecular Medicine, University of Missouri-Columbia

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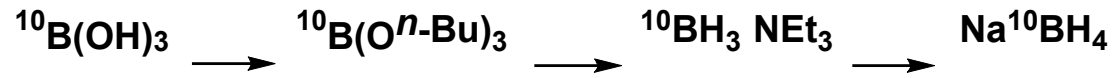
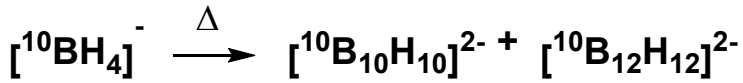
Success of BNCT directly depends on availability of ^{10}B-enriched compounds. Most of the modern BNCT agents contain polyhedral borane fragments in their structures. Polyhedral boranes are usually prepared by pyrolysis of quaternary ammonium ^{10}B-borohydrides, which in their turn are synthesized from sodium ^{10}B-borohydride. Synthesis of the latter is usually achieved via the Schlesinger procedure [1] which requires high temperatures, generates highly alkaline by-products, and is not safe to perform on a large scale using standard glass laboratory equipment.

BNCT research at the International Institute of Nano and Molecular Medicine, University of Missouri-Columbia, requires a variety of ^{10}B-enriched compounds. For convenience, we developed an alternative procedure for the synthesis of sodium ^{10}B-borohydride which uses moderate temperatures and standard laboratory equipment [2].

The production scheme starts from the commercially available ^{10}B-boric acid, $^{10}B(OH)_3$, which is through the formation ^{10}B-tri-*n*-butylborate, $^{10}B(O\textit{n}\text{-}Bu)_3$, followed by formation of triethylamine ^{10}B-borane, $Et_3N\cdot{}^{10}BH_3$, transformed into $Na^{10}BH_4$ in 60-80% total yields. This 3-step scheme was optimized to produce of 100-200 g batches of $Na^{10}BH_4$ per run.



The prepared ^{10}B-borohydride is then pyrolyzed to produce a mixture of $[^{10}B_{10}H_{10}]^{2-}$ and $[^{10}B_{12}H_{12}]^{2-}$ polyhedral anion salts.



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Accelerator-based neutron source for boron neutron capture therapy: in vitro efficacy evaluation with in-sample dosimetry using gold nanoparticles

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In BNCT, the use of an accelerator to produce neutrons instead of a nuclear reactor makes it possible to place the treatment facility in medical institutions. We evaluated the efficacy of the accelerator-based neutron source for BNCT in experiments in vitro, using animal and human cell lines and a colony-forming assay. U251MG, T98G, CHO-K1, and V79 cells were incubated with BPA containing boron-10 or boric acid at different concentrations (0, 10, 20, 40 ppm). Additionally, glycylglycine-coated gold nanoparticles were used in T98G cells to evaluate the absorbed neutron dose in the samples.

The samples were placed in a phantom made of organic glass under the lithium target of the tandem accelerator with vacuum insulation. The irradiation was performed for 1 to 2 hours with the following accelerator settings: 2.0 to 2.3 MeV proton energy, 1 to 3 mA proton current, and 50 to 300 million events of epithermal neutron generation. The activation of gold in the samples was measured using a gamma spectrometer. The accumulation of gold in the samples was observed by electronic microscopy and measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES). Using gold nanoparticle activation data, the boron dose was estimated by Monte Carlo simulation. After irradiation, the cells were seeded into 6-cm round dishes for colony formation assessment. After 1 to 2 weeks, the colonies of ≥50 cells were counted for each sample and each irradiation dose. The results were compared with controls irradiated without boron.

The cell survival data confirm the efficacy of the tandem accelerator with the lithium target to produce a sufficient number of neutrons to initiate the boron neutron capture reaction within and close to tumor cells, leading to a decrease in colony formation. The new approach in dosimetry for BNCT that we tested in the current study may allow us to determine the absorbed neutron dose using combined boron compounds containing an additional high-Z element. This approach may open up a new perspective in boron compound distribution and treatment efficacy evaluation that may lead to modification of such methods as isotope scanning and positron emission tomography (PET). A more detailed description of the results will be provided at the 17th International Congress on Neutron Capture Therapy.

Optimization of treatment procedure for hospital-installed accelerator-based BNCT: The experience of Southern Tohoku BNCT Research Center

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Introduction: Boron neutron capture therapy (BNCT) delivers the high linear energy transfer particles to tumor cells preferably without severe damage to surrounding normal tissue, and might be beneficial treatment for the inoperable case and patients who have no other treatment options. Therefore the installation of BNCT system into accessible medical institution has been desired. In our institution, the construction of Southern Tohoku BNCT Research Center (STBRC) was completed in September 2014, and the system commissioning including beam commissioning was already finished. From January 2016, a clinical study of hospital-installed accelerator-based BNCT for recurrent malignant glioma has been started. At the beginning of clinical study, we tried to optimize treatment procedure by utilizing our know-how in radiotherapy. In this presentation, I will describe the result of optimized treatment procedure.
Methods and materials: At the preparatory step for the clinical study, we considered the optimization of patient set-up and treatment planning, assuming BNCT protocol with 2-h intravenous infusion with 4-borono-L-phenylalanine (BPA) followed by neutron irradiation while continuing infusion. SERA (Simulation Environment for Radiotherapy Applications) was used for BNCT treatment planning.
Results: The optimized procedures for patient set-up and treatment planning were designed as follows. Preliminary patient set-up condition is provided from simulation by using diagnostic CT/MR image. For treatment of brain tumor, the instrument immobilizer for head fixation was newly developed assuming setup accuracy with 5 to 7 mm. For head and neck cancer, we are now developing a novel immobilizing system with set-up accuracy of 5 to 10 mm (if possible) under sitting position. After checking patient set-up condition by simulation, CT scan is performed with same patient position. Then utilization of these acquired images enables us to evaluate more realistic treatment plan. By using a 3D image analysis system that enables quick and easy access to any slice image, and using a deformable image registration system that enables more accurate fusion and image registration, which are routinely used for photon beam and proton beam radiotherapy in our hospital, any angle slice images are extracted and fitted into planning CT with realistic set-up position. Accordingly the delineation of tumor and organs at risk and the dose evaluation might be achieved with high accuracy.
Conclusions: STBRC experienced the installation of BNCT system as a medical institution for the first time in the world. Now that the cyclotron-based neutron resource is produced, it is expected that introduction of BNCT will be accelerated into other medical institutions with no experience of BNCT. Although the sufficient experience of radiation therapy helps the

installation into a medical institution, as a matter of course, the acquisition of the technical skill characteristic of BNCT treatment is one of the problems. It is thought that active technical cooperation from preceding BNCT facilities is indispensable.

A Dose Response Analysis of Head and Neck Cancer Patients Treated with Boron Neutron Capture Therapy (BNCT) in Finland

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Re-irradiation of head and neck cancer that recurs locoregionally after radiotherapy is often associated with severe side-effects. In BNCT, most of the tumor dose is derived from high-LET radiation resulting from ^{10}B neutron capture reaction [$^{10}B(n,\gamma)^{7}Li$], and a high dose gradient may be achieved between the cancerous tissue and the adjacent normal tissues provided that the boron carrier compound (e.g. L-boronophenylalanine, L-BPA) is selectively taken up by the tumor. However, tumor boron uptake often remains undefined making estimation of the delivered radiation dose uncertain. We performed a dose response analysis of a cohort head and neck cancer patients treated with BNCT in Helsinki, Finland, in 2003 to 2011.

The estimated tumor and the planning target volume (PTV) doses were correlated with the clinical tumor responses in 89 patients with inoperable previously irradiated head and neck cancer. The patients received BNCT either within a clinical trial (n=30; 29 carcinomas and 1 sarcoma) [1,2] or outside of a trial as the institute praxis (n=59; 49 carcinomas, 3 epitheliomas, 1 neuroblastoma and 6 sarcomas). L-BPA–fructose (400 mg/kg) was infused intravenously over 2 hours before neutron irradiation. Patients were treated once (n=37) or twice (n=52) with BNCT. Blood ^{10}B concentration was measured at 10-20 minute intervals during and after the BPA infusion. Neutron irradiation lasting on average 43 minutes (range, 17 to 86 minutes) was given from 1 to 3 fields when the blood ^{10}B concentration was an average of 18 µg/g (range, 10–24 µg/g). Tumor ^{10}B concentration was estimated to be 3.5 times higher in tumor than in the blood. The total photon radiotherapy equivalent dose to tumor was derived multiplying the dose components with the constant relative biological effectiveness (RBE) factors (3.2 for the proton dose components, 1 for photon dose) and for the boron dose with the compound biological effectiveness (CBE) factor (3.8) [3]. Tumor and PTV doses per fraction were correlated with the tumor response.

Twenty-six (29%) tumors responded to BNCT (complete response (CR), 20; partial response (PR), 6), 55 (62%) patients had stabilized disease (SD) for an average of 8 months (range, 1–30 months), and 4 (4%) tumors progressed. Patients with a CR or a PR had higher minimum tumor (p=0.006) and PTV (p=0.03) doses as compared with those who had SD or progressed; mean 18 Gy (W) (range, 8–34 Gy (W)) vs 15 Gy (W) (range, 7–26 Gy (W)) and mean 14 Gy (W) (range, 7–25 Gy (W)) versus 12 Gy (W) (range, 5–21 Gy (W)), respectively. Twenty of the patients who achieved a CR or a PR received BNCT twice. Three patients achieved CR after only one BNCT.

Most patients responded to BNCT or had disease stabilization for an average of 8 months. The minimum tumor and PTV doses correlated with the frequency of tumor response. Next, the BNCT doses and dose response rates will be compared with those obtained with re-irradiation using other radiotherapy techniques, and the responses reported in similar patient groups.

Enhanced Permeability and Retention (EPR) Effect-Based Efficient Boron Delivery Systems for BNCT

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Boron neutron capture therapy (BNCT) has been attracting growing interest as one of the minimally invasive cancer therapies. BSH and L-BPA have been used in BNCT for many years. L-BPA, in particular, has been widely used for the treatment of not only melanoma but also brain tumor and head and neck cancer because it can be taken up selectively by tumor cells through an amino acid transporter. The accelerator-based BNCT is now undergoing phase I/II clinical study for the treatment of brain tumor and head and neck cancer patients in Japan.

In this paper, I would like to present two strategies of boron delivery systems: liposome-based and biopolymer-based boron delivery systems. We have developed a boron-lipid-based liposomal boron delivery system (LBDS). Liposomes are efficient drug delivery vehicles because they can transport their contents to various tumors in a manner that is essentially independent of their contents. The accumulation of liposomes in tumor tissues caused by the enhanced permeability and retention (EPR) effect is based on the abnormal architectures of newly formed tumoral blood vessels that lose endothelial vessel cells without tight junctions. Although LBDS has shown promising effects in colon 26-implanted mice, a high liposome dose is necessary to deliver the required number of boron atoms to tumor. We found that the counter cations of the encapsulating boron clusters affected the liposome formation, resulting in the preparation of high boron accumulated liposomes (HBALs) by overcoming osmotic pressure limitations. Indeed, the use of spermidinium as a counter cation of closo-dodecaborates was essential to obtain HBALs with high yields. All of the mice injected with 30 mg [B] /kg body weight of HBAL were survived 100 days after thermal neutron irradiation with reducing the total amount of phospholipids less than one-seventh of those used for Na_2BSH-encapsulating liposomes.

As an alternative strategy, we focused on a serum albumin as a biopolymer. Serum albumin accumulates in malignant and inflamed tissues due to EPR effect. Furthermore, it has been observed that tumor is the major site of serum albumin catabolism, thus serum albumin has been focused on as a drug carrier. We developed maleimide-functionalized *closo*-dodecaborate (MID) to conjugate it to the serum albumin. Bovine serum albumin (BSA), chosen as a model albumin, contains 35 Cys residues and 17 disulfide bridges, and Cys34 is the only free residue among them. Surprisingly, MID was found to conjugate not only to free SH of cysteine residue but also to lysine residues in albumin under physiological conditions, forming highly boronated BSA that showed high and selective accumulation in tumor. Significant tumor growth inhibition was observed in colon 26 tumor-bearing mice subjected to thermal neutron irradiation.

Feasibility and efficacy of Boron Neutron Capture Therapy for diffused lung tumours: the Pavia University experience on the animal model

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Lung tumour, whose incidence is one of the highest worldwide, still accounts for more deaths than any other cancer in both men and women. The common form of lung neoplasm are secondary tumours, mainly from breast and colon sources. These metastases usually are disseminated or bilateral pulmonary nodules. Dissemination characterises also many of the highly heterogeneous primary lung tumours as well as malignant pleural mesothelioma. In these cases, when standard therapies, like surgery or conventional photon therapy are impracticable and chemotherapy is ineffective, no cure is available for patients. Boron Neutron Capture Therapy (BNCT) may represent an interesting alternative. Therefore, in Pavia research has been addressed to verify the feasibility and efficacy of BNCT for the treatment of disseminated lung coloncarcinoma metastases.

A suitable model of rat bearing lung metastases was set up in order to evaluate the cytokinetic of boron uptake, mediated by L-^{10}BPA, in normal (N) and neoplastic (K) lung tissues. Measurements, performed by α-spectrometry associated with neutron autoradiography, proved the selective uptake of ^{10}B by the tumour nodules with a concentration ratio K/N higher than 3. That is the basic requirement for the feasibility of BNCT. Rat lung irradiations were performed in-situ in the thermal column of the Triga Mark II Reactor of the University of Pavia, protecting the animal body inside a lithium carbonate shield, realized on purpose and following an irradiation plan calculated by Monte Carlo simulations. Groups of healthy and neoplastic rats were exposed to neutrons, with or without BPA pretreatment (300 mg/kg; i.p. 2h prior to irradiation) at the maximum reactor power of 250 kW, for fixed times of 5 or 15 minutes. Healthy animals were sacrificed within the first week post irradiation or between the eighth and tenth week; neoplastic rats within the first week, after two and after four weeks. At the autopsy, lungs and the most important radiosensitive organs (liver, heart, kidney, stomach) were explanted for histological analyses.

All the studied animals survived the prefixed irradiation treatment confirming the planned irradiation set-up and the efficacy of the designed shield for the protection of the animal organs during neutron exposure. Histological analyses performed on lungs of healthy rats groups did not evidence severe radiation damages, even at the maximum biologically tolerable weighted dose,

i.e. 7 Gy-Eq BNCT at 15 minutes of neutron irradiation. Only a mild/moderate inflammation and slight signs of fibrosis could be detected in all lung portions of the animal sacrificed at the longer period of observation. No alterations were highlighted in the parenchyma of all the other studied organs. Concerning the results of the histological analyses of BNCT treated neoplastic lung samples, geographic necrosis, extensive apoptosis and fibrosis were detected, especially for longer times of both irradiation and post-treatment observation. Further studies are in progress, addressing both late damages induced by BNCT to healthy lungs and neoplastic rats survival, in order to confirm advantages provided by BNCT in the treatment of spread lung tumours.

Re-start of Clinical and Pre-Clinical BNCT Activities at the Argentine RA-6 Nuclear Reactor

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In 2015 the Argentine BNCT project resumed its clinical and pre-clinical activities, after several years during which the RA-6 research nuclear reactor underwent significant structural modifications, extensive experimental and computational assessments, dosimetric and biological characterizations and finally, relicensing.

The new RA-6 BNCT neutron beam has a mixed thermal-hyperthermal neutron spectral composition, especially tuned for treating shallow tumors. The neutron beam port comprises a conic delimiter, which provides a flat and radially well-delimited in-air neutron flux distribution. The resulting in-phantom neutron flux attains its maximum at around 1 cm in depth and its value is about 1.05×10^9 n_{th}/cm^2s.

In the clinical scenario, and as a continuation of the phase II protocol for treating melanoma in extremities, a female patient received BPA-Fructose BNCT for the treatment of melanoma nodules in her right leg. Clinical evaluation three months later indicated that all lesions in field had positive responses and, interestingly, with the induction of vitiligo around each lesion, showed only grade 1 skin acute toxicity (erythema). No new lesions in the BNCT treated areas appeared after 35 weeks, but the patient had new lesions outside the treated area. These lesions were treated with high dose rate brachytherapy (HDR_BT), with good response, also presenting vitiligo, but in one case with greater acute toxicity compared to BNCT. Up to this point, the patient presents no evidence of nodal or metastatic disease.

With the purpose of opening a clinical protocol for treating head and neck patients in the near future, several studies are underway, including computational assessment of the efficacy of our present neutron beam, isoeffective dose calculations to predict tumor control and normal tissue complication probabilities and, recently, the beginning of a new pre-clinical protocol to treat dogs and cats with spontaneous head and neck tumors with BPA-based BNCT.

In this last context, a terminal dog with a large (approximately 100 cm^3), invasive squamous cell carcinoma in the right nasal cavity that was not amenable to surgery and was unresponsive to chemotherapy, was treated in July-August 2015 by delivering two BNCT fractions with an interval of three weeks between both applications. This strategy aimed at improving tumor control while minimizing possible dose-limiting normal tissue complications. Each fraction comprised two portals to yield the best possible CTV dose distribution. One week after the first

fraction, the dog's general condition substantially improved, nasal bleeding stopped and an evident reduction of the visible tumor mass protruding through the nasal bone was observed. One week after the second fraction the protruding tumor mass was no longer observable and the clinical status of the dog was optimum. For 8 months the dog exhibited optimum clinical signs and no protruding tumor mass. CT scans, taken a month after the second fraction showed a reduction in tumor volume of more than 50 percent. Acute toxicity after each of the fractions comprised reversible mucositis that responded to treatment with corticoids. No medium or long term toxicity was observed. Local tumor re-growth occurred 10 months after the first BNCT treatment. The dog was re-treated with 2 fractions (two portals per fraction), 3 weeks apart, of BPA based BNCT in June 2016 and to date exhibits partial tumor control and a good clinical status. The only toxic effects of re-treatment were early mild somnolence and persistent eye irritation that required treatment.

Summing up, the new RA-6 BNCT neutron beam seems to be as clinically effective as its former version for treating melanoma in extremities, but with additional advantages in its spectral characteristics. It seems also to be suitable –although it was not designed for that purpose– to treat head and neck tumors, with tailored treatment planning, for certain locations and volumes.

Patient Activation Survey for BNCT Clinical Trials at THOR

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The BNCT facility at Tsing Hua Open-pool Reactor (THOR) started the phase I/II clinical trials for patients with recurrent head and neck cancer since August 11, 2010. Up to now 22 patients have been treated. The former 17 patients were treated according to protocol 1, where each patient was irradiated by the BNCT beam for two times in a time internal of one month. The later 5 patients were treated following protocol 2, where each patient received only one BNCT irradiation and one month later additional 30 Gy dose was made up by conventional IMRT. Each BNCT irradiation was completed within ~30 minutes with a tumor target dose of around 20 Gy-eq. After BNCT irradiation each patient was measured immediately for gamma rays resulting from neutron activation of the body by using a well-calibrated portable High Purity Germanium (HPGe) detector. The measuring time is ~1200 sec and the distance between patient and detector, depending on the irradiation position, is 50 cm at the maximum. Three radioactive nuclides, namely, ^{24}Na ($t_{1/2}$=15.0 h), ^{38}Cl ($t_{1/2}$=37.3 m), and ^{49}Ca ($t_{1/2}$=8.7 m), were the dominant activation products. ^{42}K ($t_{1/2}$=12.4 h) due to the activation of naturally occurring element ^{41}K was found as well in most patients. For some patients ^{128}I ($t_{1/2}$=25.0 m) from iodine tincture wiped on the skin was found. In addition, ^{187}W ($t_{1/2}$=23.8 h), ^{199}Pt ($t_{1/2}$=30.8 m) and ^{51}Ti ($t_{1/2}$=5.8 m) from false tooth and intravascular stent were identified in several cases. Moreover, ^{56}Mn ($t_{1/2}$=2.6 h) and ^{27}Mg ($t_{1/2}$=9.5 m), possibly from dietary supplement, were measured. Dose rate as a function of time from activation products induced in the patient was evaluated by using a simplified phantom and also measured by using a survey meter. The dose rate at the surface of patient was normally lower than 100 μSv/hr at the end of irradiation and decreased to around several tens μSv/hr in 30 minutes. At one meter away from the patient's surface the dose rate dropped to below 1 μSv/hr.

PLENARY LECTURE

Nanostructured Boron Compounds: Applications in Cancer Therapy

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In recent years, much efforts have been devoted to developing nanomaterials-based boron drugs for neutron capture therapy (NCT) and to date, a majority of the studies have proved reasonably promising. Conversely, further *in vivo* studies and clinical trials are needed to establish them as appropriate boron carriers; this is especially so with the relatively novel boron nanotubes and magnetic nanoparticles. More advanced forms of boron nanotubes can be anticipated as much interest in their synthesis as their future applications. Thus, boron neutron capture therapy (BNCT) is a promising treatment for malignant brain tumors as well as for other types of cancers, such as, liver, prostate, bladder, breasts, head and neck tumors. Current research focuses on both the design and synthesis of high boron containing compounds as BNCT agents, and the search for suitable delivery vehicles. To be suitable BNCT agents, the problem of their low water-solubility needs to be resolved by chemical modification. In the case of magnetic nanoparticles, strategies are required to counter their tendency of embolization and their unclear cytotoxicity must be resolved.

Characterization of a CdZnTe detector prototype for Boron imaging by SPECT: simulations and measurements in a neutron field

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BNCT treatment effectiveness strongly depends on the radiation dose deposited locally by the $^{10}B(n,\alpha)^{7}Li$ reaction in the tumour; however, the local and real time measurement of this quantity during the neutron irradiation is a big challenge, not yet solved by the BNCT researchers' community.

The deposited dose evaluation needs a correct knowledge of the ^{10}B concentration spatial distribution and the thermal neutron flux in the tissue at the irradiation time. In order to solve this problem it is possible to exploit the 478 keV dis-excitation photons of the ^{7}Li and as such avoid the difficulty of measuring the Boron concentration and the neutron flux as separated quantities. Therefore our project aims to develop a Single Emission Computed Tomography (SPECT) system based on a CdZnTe (CZT) semiconductor detector to be installed at a new BNCT clinical facility.

Room-temperature semiconductor detectors, such as CZT, have favourable physical characteristics for medical application, moreover the material is present on the market at affordable prices and generally shows very good energy resolution, e.g. the characterization measurements carried out on our prototype estimated an energy resolution of 2.6% at 661 keV energy. With further development it is possible to create a 3D imaging detector with very high energy and spatial resolution, operating on the 100-700 keV energy range.

Here we show the characterization results of a CZT prototype (5x5x20 mm^3): first we studied its response to standard calibration gamma sources and then we measured the detector's performances in presence of a neutron field, such measurements were conducted in the thermal column of the Triga Mark II reactor. The 478 keV line due to the $^{10}B(n,\alpha)^{7}Li$ reaction was clearly visible. In both cases the experimental set up was also simulated by the means of the MCNP Monte Carlo code.

Moreover to study the pre-clinical application of the CZT SPECT system we simulated, using GEANT4, the setup needed for measurements on small animals using a PMMA phantom and setting the detector at different distances from the PMMA phantom axis; to carry out this study we used an epithermal neutron spectrum simulated by our team for an accelerator based clinical facility.

In the talk these preliminary results and the possibilities for further studies will be shown.

Synthesis of Cobalt and Iron Bis(dicarbollide) Derivatives for Potential BNCT Application

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The subject of this lecture is our recent results on the synthesis of cobalt and iron bis(dicarbollide) anions [3,3'-M(1,2-$C_2B_9H_{11})_2]^-$ conjugates with porphyrins and phthalocyanines and investigation of their interaction with cancer cells in order to find compounds for potential BNCT application. Conjugation of polyhedral boron hydrides with porphyrins is an attractive way to create dual agents for anticancer boron neutron capture therapy (BNCT) and photodynamic therapy (PDT). The 1,4-dioxane derivative of cobalt bis(dicarbollide) reacts with amino derivatives of chlorin e_6 prepared by the *E* ring cleavage in pheophorbide *a* methyl ester with α,ω-diaminoalkanes. This reaction leads to preparation of the conjugates of chlorin e_6 and cobalt bis(dicarbollide) with $NH(CH_2CH_2)_nNH_2$ + $(CH_2CH_2O)_2$ (n = 1, 2, 3) spacers between them. An interaction of these conjugates with human lung adenocarcinoma A549 cells were studied, namely, ability of conjugates to penetrate in cells, intracellular distribution and localization, quantitative characteristics of intracellular accumulation. Based on these data the most promising conjugates for BNCT are described. We report on breakthroughs in the structural optimization of conjugates of chlorin e_6 derivative with bis(dicarbollide)cobalt. One of these conjugates (where n=3) dimethyl ester of 13-carbomoylchlorin e_6 [N-hexylamine-N'-ethoxyethoxy]-cobalt-bis(dicarbollide) (conjugate **1)** is able to accumulate quickly and efficiently (distribution factor of 80) in cancer cells, thus delivering more than 10^9 boron atoms per cell when its extracellular concentration is more than 1 μmol L^{-1}. Also **1** is an active photosensitizer and phototoxic towards human lung adenocarcinoma A549 cells at 80 nmol L^{-1} (50% cell death). Photo induced cytotoxicity of **1** is associated with lipid peroxidation, lysosome rupture and protease activity enhancement. Conjugate **1** fluoresces in the red region (670 nm), which is useful to monitor its accumulation and distribution *in vivo*. It is not toxic to cells without activation by neutrons or photons. The properties of **1** warrant its preclinical evaluation as a multifunctional agent for BNCT, photodynamic therapy and fluorescent tumor diagnosis. The similar conjugate with iron bis(dicarbollide) anion [3,3'-Fe(1,2-$C_2B_9H_{11})_2]^-$ was prepared as well. Its biochemical properties are close to those found for the cobalt bis(dicarbollide) conjugate **1**. The reaction of 1,4-dioxane derivative of cobalt bis(dicarbollide) with tetradihydroxyphenoxy substituted Zn(II)-phthalocyanine leads to the new highly boronated Zn(II)-phthalocyanine with eight cobalt bis(dicarbollide) units (144 boron atoms) and its intracellular accumulation and distribution in GL6 human glioblastoma cells were studied. It was found that the boronated phthalocyanine undergoes strong aggregation in intracellular environment.

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An Effective Therapeutic Method for Treating Multifocal Liver Tumor: Boric Acid-mediated BNCT in VX2 Liver Tumor-bearing Rabbit Model

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Introduction: Hepatoma is a lethal malignancy with poor prognosis and presents as multifocal tumors in more than 80% of the patients. It is the second leading cause of cancer deaths globally. Current therapies have limited efficacy. Boron neutron capture therapy (BNCT) is an internal target radiotherapy, which enables the area of boron neutron capture reaction to be selected may succeed in hepatoma therapy. In current BNCT for liver tumor, the suitable boron delivery agent is the key element. In this study, ^{10}B-enriched boric acid (99% ^{10}B, BA) was found to be a potential boron drug for hepatoma; the selective accumulation of BA and the therapeutic efficacy of BA-mediated BNCT were investigated in a liver tumor-bearing rabbit model.

Materials and Methods: A VX2 multifocal liver tumor-bearing rabbit model was established; each tumor-bearing rabbit received two fractions of BA-mediated BNCT at the Tsing Hua Open Pool Reactor. The rabbits were intravenously injected with BA (50 mg ^{10}B/kg BW). Boron concentration was measured by ICP-AES analysis. Pharmacokinetic analysis was performed to determine the optimal time interval for neutron irradiation, while computed tomography scanning and ultrasound imaging were used to measure the localization, size, and blood supply of the tumors. The microdistribution of boron in tumor-bearing liver was also investigated by neutron capture autoradiography. The physical dose of radiation was calculated using Monte Carlo N-particle code.

Results: Autoradiography revealed that BA was highly targeted in the tumor mass and the tumor blood vessels; a low density of alpha tracks was observed in normal liver tissue. The ratio of track density in the tumor and the tumor vessels to that of adjacent normal liver tissue was 2.5±0.5. Ten rabbits with 28 tumors were treated with two-fraction BNCT. The physical dose administered to the tumors ranged from 6 to 16 Gy in the first BNCT fraction and 6 to 11 Gy in the second BNCT fraction. Obvious reductions of tumor size and blood flow were detected following the first fraction of BNCT treatment. The second BNCT treatment was performed on the 20th day after the first treatment. The size of the tumor continued to decline thereafter and the blood flow around the tumor was completely restricted following the second BNCT treatment. After receiving two-fraction BNCT treatment, the physiological conditions of each test subject

remained good, and the tumors continued to shrink; 93.75% of the tumors had completely disappeared after two fractions of BA-mediated BNCT. Histopathologic investigation demonstrated a complete regression of tumor in any livers.

Conclusion: This investigation reveals that BA is highly targeted to liver tumors and tumor vessels, and the multifocal liver tumors can be successfully cured by BA-mediated BNCT. The killing of tumor cells and the disruption of tumor blood vessels while normal tissues are spared, may be responsible for the success of BA-mediated BNCT for liver tumors.

The first NCT clinical trial of skin melanoma at In-Hospital Neutron Irradiator

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Introduction

A Phase I/II protocol for treating cutaneous melanomas with BNCT at In-Hospital Neutron Irradiator(IHNI) was designed in China by The Third Xiangya Hospital, cooperated by BCTC, 401 Hospital, CIAE and CZEC. The protocol was designed to evaluate the efficacy and toxicity of BNCT for skin melanomas.

Materials and methods

Case1, male, 53-years-old, had superficial spreading malignant melanoma on the sole and heel of his left foot. Case 2, female, 32-years-old, had acral lentiginous melanoma on her right thumb under the fingernail. Case3, male, 50-years-old, had multiple metastatic nodular melanoma on right leg.

The boron delivery agent included in the protocol was the boronophenylalanine-fructose complex (BPA-F), produced by Syntagon AB, Sweden. BPA-F injection was infused intravenously over 90 min at a 350mg/kg B.W.. The normal skin was considered the organ at risk and the maximum tolerable dose for this organ is considered the therapeutic dose. Normal skin maximum dose of 16.0 Gy-eq and a minimum dose for tumor control of 20 Gy-eq were assumed.

IHNI was specially designed neutron source for BNCT, with thermal power of the reactor is 30kW.The thermal neutron beam of IHNI was use in this protocol. Dosimetry calibration of this beam concerned both computations and measurements performed with the MCNP5 radiation transport code, and measurement in cubic PMMA phantom.

A BPA-F injection uptake study was taken four day before the treatment to obtain the biodistribution of ^{10}B in blood, normal tissue and tumor.Blood samples were taken every 15 or 30min for 360 min. Samples of normal tissue and tumor were taken by surgery, 0.5h and 1h after the end of BPA-F injection. The ^{10}B concentration was measured with ICP-AES method. The open 2-compartment mode was employed to fit the boron concentration measurements in blood.

Dose calculations and treatment plan evaluation were performed using the MCNP simulation. Based on the CT of the patient's extremity and a tissue equivalent digital phantom, a treatment time-^{10}B concentreation-OAR dose table was calculated. A set of TLD700 was used to estimate the gamma-ray dose distribution of different part of the patient during the irradiation.

Three patients received four times treatments and totally 7 irradiation fields with the beam aperture diameter of 6cm or 10cm, and the irradiation time was between 9.7min to 19min for each field during Sep 2104 and July 2015. All these four times treatments were follow the same therapeutic regimen as mentioned above.

Results

The tumor response was assessed clinically by inspection and other clinical examination. For all three patients four times treatment, only grade 1 RTOG/EORTC skin acute reaction was detected after the treatment. Case 1 showed complete clinical response (CR) four weeks after the second treatment. Case 2 and Case 3 showed partial clinical response.

Conclusion

First three BNCT treatments of a skin melanoma at In-Hospital Neutron Irradiator in China were successfully performed with good clinical response and low toxicity. Further study in large number of patients is needed for long-term outcome.

Items Layout of Nuclear Medical Ship for Neutron Capture Therapy (NCT) Clinical Studies and Trials

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Abstract: Neutron Capture Therapy (NCT) has had a history of 65 years and neutron sources for NCT are all from nuclear reactors. No clinical event due to fault of nuclear reactor or neutron beam has been reported so far. There used to be 15 NCT clinical centers with neutron beams led out from nuclear reactors in the world, but unfortunately, some large and medium sized nuclear research reactors have been decommissioned in concomitance with their life span termination or closed down due to the aging facilities. At present time, there are very few NCT clinical centers left, and such a situation accounts for a setback of NCT development in a real sense. We have been engaged in development studies of items layout in an ocean-going nuclear medical ship (NMS) for NCT application in 2010, when the specially designed In-hospital Neutron Irradiator (IHNI) for BNCT clinical studies and trials in China completed its construction. Nowadays, the conception design has been done. The objective of our studies is to provide NCT chance to those cancer patients in non-nuclear countries. The NMS named “Star of Hope” is equipped with NCT and the advanced conventional radiation therapy facilities mainly for clinical trials of breast cancer patients. The major therapeutic facility is a set of neutron source nuclear reactor system, which is the modified version of land-based IHNI called Cancericidal Nuclide Neutron Knife (CNNK) and located in the NMS cabin. With a reactor power of 30kW, the IHNI has been put into operation and used for clinical irradiation to three patients with acral lentiginous melanoma (ALM). The updated CNNK has a reactor power up to 36kW with two neutron beams i.e. one mixed beam with a thermal neutron flux of (1-2) E+9n·cm^{-2}·s^{-1} and an epithermal neuron flux of (2-4) E+8n·cm^{-2}·s^{-1} at the port, the other is an epithermal beam with a neutron flux of $\geqslant$6 E+8n·cm^{-2}·s^{-1} at the port. The design of the two neutron beams is able to generally meet requirement of clinical irradiation at breast cancer foci. Driven by integrated full electric propulsion system, the NMS has been designed suitable for ocean-going voyage. The length of the ship is 89m, breadth molded 17m, draught 5.5m, gross tonnage 5,500t approx., endurance 10,000 nautical miles and 60 days, with a complement of 90 persons. Operation modality of the NMS: performing BNCT clinical trial at anchor port and conducting BNCT studies while sailing at sea. The NMS has also equipped with a telemedicine system and a helicopter.

Targeting the Glioma Hypoxic Tumor Microenvironment with a Novel Boron Neutron Capture Therapy Agent

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Introduction: Glioblastoma multiforme (GBM) represents the most common primary brain tumor among adults. Despite current aggressive chemoradiotherapy regimens, the overall survival remains exceedingly poor in these patients. The high recurrence rate observed in GBM is in part attributed to the hypoxic tumor microenviroment. Tumor hypoxia has been shown to increase metastasis, promote angiogenesis, and confer resistance to chemotherapy and radiation. While boron neutron capture therapy (BNCT) has the potential to become a cancer treatment alternative, more selective agents are needed to promote its clinical translation. In order to sensitize the hypoxic and often therapy resistant hypoxic tumor microenviroment to BNCT, a novel nitroimidazole derivative has been developed capable of targeting hypoxic GBM cells.

Materials and Methods: A 2-nitroimidazole derivative B-381 has been synthesized in a single step reaction. The *in vitro* cytotoxicity and cellular accumulation of B-381 in glioma cell lines (D54 and U87) has been evaluated under normoxic and hypoxic conditions compared to L-boronophenylalanine (BPA). Using an *in vivo* glioma tumor model, the long-term tumor retention of B-381 was evaluated.

Results: B-381 demonstrated low cytotoxicity in normal and cancer cells. Unlike BPA, B-381 illustrated preferential retention in hypoxic glioma cells compared to normoxic glioma cells and normal tissues *in vitro*. *In vivo*, B-381 illustrated significantly higher long-term tumor retention compared to BPA, with 9.5-fold and 6.5-fold higher boron levels at 24 and 48 h, respectively.

Conclusions: B-381 represents a new class of BNCT agents in which their selectivity to tumors is based on a hypoxic tumor metabolism. Further studies are warranted to evaluate this compound and similar compounds as preclinical candidates for future BNCT clinical trials in the treatment of glioma.

BNCT Laboratory in BINP

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A source of epithermal neutrons based on a tandem accelerator with vacuum insulation and lithium target was proposed and constructed in BINP for development of boron neutron capture therapy of malignant tumors. In 2014, with the support of the Russian Science Foundation BNCT laboratory was created in order to be ready to implement BNCT by the end of 2016. The laboratory was equipped by wire scanner probe OWS-30 for ion beam profile measure, activation foils kits SWX-1552 for neutron spectra measure, beam shaping assembly with magnesium fluoride moderator and graphite and lead reflector for neutron beam form, simultaneous ICP atomic emission spectrometers ICPE-9820 for multiple elements analyze and so on. Over the last year the unwanted flow of charged particles in an accelerator was studied and suppressed, its high-voltage strength was improved and proton beam current was increased from 1.6 mA to 5 mA that is sufficient for BNCT. Prolonged stable generation of neutrons with an average current of protons 2.5 - 3 mA was implemented. The effect of neutron radiation on different cell cultures incubated in boron medium, and the viability of the mice grafted with tumor was studied. Fluence of protons leading to the appearance of blisters on the substrate of the neutron generating target was detected. The report presents and discusses the results of the research and declares further plans.

Present status of BNCT System using 30 MeV Cyclotron

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Sumitomo Heavy Industries (SHI) is now producing medical devices, such as PET system and Proton Therapy System, based on a-half-century history of manufacture of particle accelerators. From 2006, SHI started the development of a neutron source for BNCT based on a 30 MeV cyclotron. By collaboration with Kyoto University Research Reactor Institute (KURRI), the BNCT system was installed at KURRI campus in 2009. After the non-clinical tests were completed, the Phase I clinical trial was started in corporation with STELLA PHARMA CORPORATION for recurrent brain tumor in 2012. Also, the Phase I clinical trial for recurrent head & neck cancer was started in 2014. In parallel with the clinical trials, the construction of the same system at another site was started. The site is Southern Tohoku BNCT Research Center (STBRC) at Fukushima prefecture in Japan, and the construction was completed in 2014. From 2016, phase II clinical trials for recurrent brain tumor and head & neck cancer have been started. BNCT has been treated at both KURRI and STBRC.
Overview of the projects and details of the cyclotron based BNCT system will be presented.

BNCT for Malignant Brain Tumors, from Reactor to Accelerator

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Since January 2002, we applied BNCT for malignant brain tumors. As of May 2014, we have applied reactor-based BNCT for 58 cases of newly diagnosed GBM, 50 cases of recurrent malignant gliomas, 32 cases of recurrent high grade meningiomas, and so on, totally 148 cases with 167 times BNCT. In this talk, let us focus our efforts on chiefly BNCT for recurrent malignant gliomas for these 14 years.

At first we applied BNCT for recurrent malignant gliomas using BSH and BPA simultaneously with the simulation by F-BPA-PET, as a clinical study. On neuro-images including contrast enhanced CT or MRI, marked early shrinkage of the enhanced lesions or perifocal edema were obtained from these initial studies. More than 50% of the contrast-enhanced lesions disappeared in 8 out of the initial 12 recurrent malignant glioma patients during the follow-up period. Then we assessed the survival benefit of treating recurrent malignant gliomas with BNCT. To evaluate this benefit in the low and high risk group of recurrent malignant gliomas, we adopted the recursive partitioning analysis (RPA) classification for recurrent malignant gliomas advocated by Carson et al. in a 2007 article in the Journal of Clinical Oncology. When we published our initial results of BNCT for recurrent malignant gliomas, survival data was analyzed using 22 consecutive cases of recurrent malignant gliomas treated by BNCT from 2002 to 2007. BNCT could prolong the survival of recurrent malignant gliomas, especially for high risk group markedly.

As to recurrent malignant gliomas, all cases received some radiation therapy, prior to BNCT, therefore radiation necrosis was inevitable even after tumor-selective particle radiation, BNCT. Therefore, we applied anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab aggressively for the treatment of symptomatic radiation necrosis after BNCT especially for the recurrent cases who had already treated by other radiation modality. This treatment contributed to further improvement of patient survival of recurrent malignant gliomas after BNCT.

Depending on these experiences of reactor-based BNCT, we started a phase I clinical trial using both new BPA compound and a new neutron generator, cyclotoron-based accelerator, for recurrent malignant since 2012. This study was aimed for the safety and tolerability of this treatment. The clinical trial enrollment and observation were finished with a favorable result. Now we are doing a phase II clinical trial for recurrent GBM using the same combination to clarify the effectiveness. In this talk, let me introduce the protocol and interim analysis of these trials.

Preliminary study on feasibility of boron neutron capture therapy in patients of diffuse intrinsic pontine glioma without craniotomy

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Introduction

Diffuse intrinsic pontine glioma (DIPG) has been a very frustrating disease for patients, family, and doctors. Boron neutron capture therapy (BNCT), as a targeted radiotherapy, might carry potential to project adequate radiation dose to the tumor cells while sparing normal brain stem.

Materials and methods

In this study, simulation computerized tomography (CT) of consecutive 12 patients with DIPG treated with external beam photon radiotherapy in Taipei Veterans General Hospital during 2008 and 2016 was used with NCTplan v.1.1 to estimate the radiation dose to the pontine tumor and surrounding normal tissues irradiating from 4 portals with equal weighting. The ages of patients were between 4 and 53 year-old, with median of 10 year-old. The default neutron energy and flux was 1.2 MW and 9.4E+08($n \cdot cm^{-2} \cdot sec^{-1}$), respectively. RBE of photon dose, ^{10}B dose, thermal neutron dose and fast neutron dose were 1, 1.35, 3.2, 3.2, respectively, in normal tissue, and 1, 3.8, 3.2, 3.2, respectively, in tumor. Prescribed dose was 20 Gy(w) received in 80% volume. Tumor/normal tissue (T/N) ratio between boron concentrations was assumed to be 3.5.

Results

The ratio of minimal dose to the tumor and maximal dose to normal tissue was between 1.81 and 2.62, with an average of 2.26. Ten of the 12 patients achieved a ratio greater than 2. The mean dose to whole brain was between 4.03 Gy(w) and 5.22 Gy(w), with an average of 4.59 Gy(w). The maximal dose to normal brain was between 7.26 Gy(w) and 9.36 Gy(w), with an average of 7.71 Gy(w).

Conclusion

Therapeutic benefits might be achieved using four-ports BNCT in patients with DIPG.

Feasibility Study of Boron Neutron Capture Therapy for the Treatment of Osteosarcoma

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Osteosarcoma is the most frequent primary malignant bone tumour, and its incidence is higher in children and adolescents, for whom it represents more than 10% of solid cancers. Despite the introduction of adjuvant and neo-adjuvant chemotherapy that markedly increased the success rate in the treatment, aggressive surgery is still needed and a considerable percentage of patients do not survive due to recurrences or metastases. Being a tumour that affects preferentially a young age population, the psychological and social cost of the treatment is still very high. Osteosarcoma is an infiltrative tumour. Thus, a negative surgical margin is the requirement to reduce undesirable tumour spreads associated with a very poor prognosis. For this reason, BNCT is studied as an adjuvant therapy that would allow for a less aggressive surgery by selectively killing infiltrated tumour cells in the surrounding healthy tissues.

In Italy, a Radio Frequency Quadrupole (RFQ) proton accelerator has been designed and constructed for BNCT. A Beam Shaping Assembly able to shape a neutron spectrum with a peak between 1 and 10 keV was numerically achieved and treatment planning simulations were carried out to evaluate the dose distribution obtained in clinical cases of limb Osteosarcoma. Thus, the neutron beam was tailored to obtain the most advantageous dose distribution in limb tumours and in surrounding tissues.

The feasibility to effectively treat Osteosarcoma depends on the boron concentrations achieved in tumour and in normal tissues. In Pavia, measurements by nuclear methods have been carried out to establish boron uptake in relevant tissues of a rat model bearing limb Osteosarcoma. A work is ongoing to measure boron also in normal bone, a hard tissue more difficult to prepare for charged particle spectrometry and neutron autoradiography. Results obtained so far demonstrate that BPA is selective for Osteosarcoma, allowing for concentration ratios higher than 3.

Dosimetry has been assessed using both the standard fixed RBE/CBE weighted-dose formalism (*Equivalent Dose*) and the photon iso-effective dose model. Both the RBE/CBE values and the parameters of iso-effective dose were determined from UMR-106 Osteosarcoma cell survival curves, assessed by neutron irradiation at the TRIGA reactor of Pavia University (with and without BPA treatment) and by gamma irradiation at S. Matteo Polyclinic Foundation, Pavia. The formalism of photon iso-effective dose has demonstrated to derive more suitable results when dose-effects of BNCT are compared to those obtained with conventional photon therapy. Therefore, this dose model and the parameters derived from the survival curves measured in Pavia were applied to re-calculate the treatment planning of the limb Osteosarcoma.

The first patient with this malignancy has been treated with BNCT in Kyoto, Japan. A radio-induced skull Osteosarcoma was irradiated at Kyoto University Research Reactor Institute. In light of a successful result (tumour control and no adverse effects), the dosimetry of the limb patients was compared to the doses obtained in the clinical case. For this, the latter were evaluated retrospectively using the fixed RBE/CBE weighted-dose and the photon iso-effective dose models based on the survival curves of UMR-106 Osteosarcoma cell line.

Towards ^{10}B neutron capture reaction mapping in a patient with photon-counting SPECT systems

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Introduction: The determination of the boron distribution in the patients' tumor and surrounding tissues during the treatment has been a challenge in boron neutron capture therapy (BNCT). A solution to determine ^{10}B concentrations as well as the dose due to boron neutron capture reaction during neutron irradiation could be Photon-Counting Single Photon Emission Computed Tomography (PC-SPECT) technique. PC being energy discrimination of the detected spectrum, which can be realized with CdTe spectrometers. We present here the results of a virtual CdTe based PC-SPECT system that shows the principal functionality of the approach and compare the results to simulations. Additionally, the signal dependency of the ^{10}B concentration has been investigated and compared to simulations.

Materials and Methods: The study was performed at the FiR 1 research reactor in Espoo, Finland. The CdTe spectrometer has an energy resolution capable of distinguishing signals from both the ^{10}B(n,γ) and ^{113}Cd(n,γ) reactions. Both signals can be used to improve determination of the ^{10}B distribution instead of relying on the ^{10}B(n,γ) signal only. Targets of different ^{10}B concentrations (100 μg/g and 400 μg/g) were placed in a cylindrical plastic phantom (length 20 cm, radius 10 cm) and irradiated with the epithermal neutron beam at 0.25 kW reactor power (0.1% of the full power of FiR 1). The higher concentration target was successfully detected in an earlier study with similar setup. Spectra of this target were collected at several positions along the phantom axis (equivalent to beam axis) and radial distances from the phantom. Collected data was combined to create a virtual line detector along the phantom axis. The lower ^{10}B concentration target was used to investigate the system performance closer to clinical situation. The results were compared to simulations performed with MCNP5.

Results: The axial scan reveals an expected dependency of the signal on the depth of boron target within the phantom. The results suggest that using signals from the ^{10}B(n,γ) and ^{113}Cd(n,γ) reactions improve the accuracy to determine the target location. Furthermore our results indicate that ^{10}B levels as low as 100 ppm can be detected when using both the ^{10}B(n,γ) and ^{113}Cd(n,γ) signals.

Conclusion: We have shown that a PC-SPECT system based on a CdTe spectrometer can principally be used to determine the location and concentration of a ^{10}B target within a phantom. The system is highly sensitive due the high detector efficiency and simultaneous detection of gammas from the ^{10}B(n,γ) and ^{113}Cd(n,γ) reactions, which allows further development towards real time ^{10}B mapping in a patient during or before and after the BNCT treatment irradiation.

Clinical results of reactor-based BNCT using BPA for the patients with recurrent malignant glioma

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We have treated a group of >150 patients with high grade gliomas / meningiomas with BNCT. Our past study with modified BNCT was characterized as simultaneous use of sodium borocaptate (BSH) and boronophenylalanine (BPA), both of which have been used clinically. Successful BNCT depends on the distribution of boron containing drugs in both tumor and normal tissue. We also used ^{18}F-labeled BPA positron emission tomography (FPBA-PET), especially for the patients with recurrence after irradiation and irradiation dose was calculated from FBPA-PET and blood sampling. For the recurrent malignant glioma (MG) cases, the median survival time (MST) was 11 months (m) while that of NABTT cases was 7m. Based on the NABTT RPA classification (JCO, 2007), BNCT showed good survival benefit especially for the poor prognostic group (RPA class 3+7) from 4.4m (NABTT) to 9.6m (after BNCT).

Recently, we did the phase 2 clinical study of reactor-based BNCT using single boron containing drug, BPA, for recurrent malignant glioma with modification of administration. Recurrent MG patients (on-site histology; WHO grade III or IV) are eligible for this study.

Twenty-three patients were treated by this protocol with reactor epithermal neutron. Average tumor volume was 32mL and average depth of the targeted lesion was 57mm from skin surface. Thirteen patients were classified for RPA class 3+7. Boron concentration in the tumor was 106 ppm and blood was 27 ppm. The minimum tumor dose was calculated as 40 Gy-Eq and maximum brain dose was 10.5 Gy-Eq. Median survival was 11.6 (95%CI: : 7.6-16.5) months after BNCT with 6- and 12- month survival of 74 and 42%, respectively.

The prognosis of recurrent malignant gliomas (MGs), especially glioblastoma is still poor. The standard treatment for recurrent MG has not yet been established. In most cases, a full course of radiotherapy has been applied after primary diagnosis; therefore, application of re-irradiation has to be applied with caution. With recent technical advancement, radiation therapies have enabled to deliver high local doses as an effective salvage treatment with low rates of side effects. However, even if the radiographically remaining, progressed tumor could be targeted with higher irradiation doses, there is still remaining problem to be solved with the tumor with highly infiltrating / invasive nature or surrounding functional organ at risk for re-irradiation. BNCT might be overcome this problem with acceptable toxicity and give a survival benefit for these patients.

Time course changes in ^{18}F-BPA uptake dynamics by PET scan

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Introduction: ^{18}F-fluorinated boronophenylalanine positron emission tomography (^{18}F-BPA-PET) scan is used for determination of indication of boron neutron capture therapy (BNCT). But some inflammatory tissues uptake ^{18}F-BPA, which makes it difficult to distinguish mere inflammation from the existence of active tumor by ^{18}F-BPA-PET scan. The purpose of this study was to search the method of estimating tumor activities by ^{18}F- BPA-PET scan.

Materials and Methods: 102 examinations of ^{18}F-BPA-PET scan was performed between 2012 and 2015 at our hospital. Among these patients, those who underwent ^{18}F-BPA-PET scan more than once were selected and focused on the difference in ^{18}F-BPA uptake dynamics between respective PET examinations. In each examination, continuous ^{18}F-BPA uptake data were acquired for 60 minutes after the injection of ^{18}F-BPA. ^{18}F- BPA uptake dynamics were evaluated by calculating maximum standardized uptake value (SUVmax) every 10 minutes by the image-analysis software.

Results: 8 patients were selected who underwent ^{18}F-BPA-PET scan more than once. Three, four, and one patient experienced two, three, and five times of ^{18}F-BPA-PET scan. All 8 patients were male and their ages at the first ^{18}F-BPA-PET scan ranged 15-63 (median 32) years. Five patients underwent BNCT after first application of ^{18}F-BPA-PET. Other three patients received proton beam therapy, CyberKnife radiosurgery, or only chemotherapy. ^{18}F-BPA uptake patterns can be divided into 2 groups; early peak pattern and delayed peak pattern. For the early peak pattern, SUVmax reached a peak within 10-30 minutes after injection, and it was stable or decreased thereafter along the time course. For the delayed peak pattern, SUVmax moves up gradually up to 60 minutes. ^{18}F-BPA uptake dynamics for their first-time ^{18}F-BPA-PET scan were early peak patterns in all but one patient, and the other patient exhibited delayed peak pattern. Among these 8 patients, ^{18}F-BPA uptake pattern changed after treatment in 3 patients. All these 3 patients received BNCT. Two patients were early peak pattern before treatment, and the other were delayed peak pattern. For the 5 patients, ^{18}F-BPA uptake pattern did not change after treatment, although SUVmax fell down by their treatments. In the patient with external auditory anal cancer, ^{18}F-BPA uptake dynamics changed from early peak pattern to delayed peak pattern after BNCT. Histopathological examination after BNCT revealed no surviving cancer cells remaining in the necrotomy specimen in this patient.

Conclusion: Early peak pattern of ^{18}F-BPA uptake dynamics appears to reflect active tumor tissues in ^{18}F-BPA- PET in most cases, and delayed peak pattern may be indicative of inflammations. Changes in the uptake pattern after treatment might represent good treatment responses in ^{18}F-BPA-PET scan.

Cerebrospinal fluid (CSF) dissemination of malignant gliomas following treatment with boron neutron capture therapy (BNCT)

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Introduction

Despite current standard therapy, the prognosis of patients with malignant glioma (MG) remains poor. We have used boron neutron capture therapy (BNCT) to treat patients with either recurrent or newly diagnosed MG. BNCT resulted in a significant increase in median survival (MeS) of patients with newly diagnosed MG to 15.6 months (protocol 1 + 2) and 23.5 months (protocol 2), and to 9.1 months for
partients with recurrent MG [*J. Radiat. Res.* (2009) 50: 51–60; *J.Neurooncol*. (2009) 91: 199–206]. More than 85% of glioblastoma (GBM) patient tumor recurrences following standard treatment are within 2 cm of the original margin of the contrast-enhancing lesion as determined by MRI. In our clinical trial of BNCT, the most frequent cause of death after BNCT has been cerebrospinal fluid (CSF) tumor dissemination and the MeS following this has been 4.8 mo. However, local control of MGs by BNCT has been significantly better than current standard therapy. The purpose of the present study was to determine if there were specific histopathologic types of MGs that were more likely to disseminate to the CSF following BNCT.

Materials and Methods

The study group consisted of 87 patients with supratentorial MGs consisting of GBMs, anaplastic astrocytomas, anaplastic oligodendrogliomas or anaplastic oligoastrocytomas who had received BNCT at the time of tumor recurrence and 41 patients with newly diagnosed GBM treated with BNCT. All were treated between January 2002 and July 2013. Tumor histology and immunohistochemical staining for two molecular markers, Ki-67 and $IDH1^{R132H}$, were evaluated for 20 of the 30 patients who developed CSF dissemination following BNCT.

Results

The gross pattern of dissemination was determined in 28 patients. Among these, 8 had local recurrence plus dissemination to the cranial subarachnoid space, 18 recurred only in the cranial subarachnoid space, and 2 to the spinal cord. Histopathologic examination revealed that 10 of the 20 tumors were histologically small cell predominant GBMs and three were oligodendrogliomas (two of which were grade III) comprising 65% of the total. Six of the seven remaining tumors were histopathologically classified as GBMs and one was classified as a gliosarcoma. Four of the 20 tumors were strongly (+) for immunostaining for the R132H mutant of isocitrate dehydrogenase (IDH^{R132H}). Immunohistochemical staining for Ki-67, a marker of cellular proliferation, was quite variable and ranged from 2–75%, with the highest positivity noted for those tumors composed mostly of small cells.

Conclusions

The present study suggests that histologically small cell glioblastomas, and possibly oligodendrogliomas, disproportionately accounted for patients who had CSF dissemination. The reasons for this are unclear, but suggest that such tumors might have an increased propensity to spread to the CSF following BNCT, the possible mechanisms for which are yet to be determined.

Case experience of boron neutron capture therapy for radiation-induced cranial osteosarcoma

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Introduction: Radiation-induced osteosarcoma; RIOS of the head is a devastating complication of radiation therapy. It is very rare but aggressive, with high recurrence rate and a poor prognosis. The median overall survival time was reported to be 29 months. Osteosarcoma is thought to be radio-resistant. Therefore, complete surgical resection has been described as the most important prognostic factor and the first choice of treatment for RIOS. If complete surgical resection is difficult, adjuvant chemotherapy and radiotherapy should be considered. These therapeutic effects have thus far been found to be insufficient, however. We report here the case of a patient with recurrent RIOS who was treated effectively by boron neutron capture therapy (BNCT).**Materials and Methods:** A 54-year-old Japanese female was referred to our institute for treatment by BNCT of a recurrent RIOS involving the left occipital bone. The patient could not walk because of acutely developing cerebellar ataxia. We performed BNCT for the RIOS because the lesion/normal brain (L/N) ratio of fluoride-labeled boronophenylalanine positron emission tomography (FBPA-PET) was enough high (L/N ratio: 5.0). For the BNCT, neutron irradiation was applied at Kyoto University Reactor. The patient was administered 500mg/kg of BPA intravenously for 3.2 hours (200mg/kg for initial 2 hours, prior to neutron irradiation, 100mg/kg for 1.2 hours during neutron irradiation). For this patient, we estimated that the minimum tumor and maximum normal brain and skin doses were 67.7, 12.7 and 12.4 Gy-Eq, respectively in the BNCT, simulated from F-BPA-PET imaging and the blood BPA concentration. **Results:** At only 3 weeks after the BNCT, the patient was able to walk again stably without aid. The subcutaneous tumor was reduced dramatically without radiation injury of the scalp, with time after BNCT. The only adverse effect was hair loss in neutron-irradiation field. MRI showed the further reduction of tumor and the disappearance of the cerebellar edema, 3 months after BNCT. Also F-BPA-PET taken 2 months after BNCT showed faint tracer uptake (L/N ratio:1.2), indicating some metabolic change at least by this treatment. Chest CT showed multiple metastatic pulmonary nodule 10 months after BNCT. They were reduced by chemotherapy using carboplatin and etoposide. MRI showed cerebral edema and contrast enhancement in left temporal lobe and occipital lobe 11 months after BNCT. They were reduced by administration of bevacizumab. Unfortunately, 17 months after BNCT, she died of re-worsening of pulmonary lesions after chemotherapy, without any deterioration of the skull lesion.

Conclusions: We experienced only a case of successful treatment of BNCT for RIOS. BNCT is an effective treatment for non-resectable RIOS. We suggest that BNCT is the only effective therapy for tumors that have invaded the skin and venous sinuses.

Boron neutron capture therapy in skull base high-grade meningioma

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Introduction: Boron neutron capture therapy (BNCT) is form of tumor-cell selective particle irradiation using low energy neutron irradiation of non-radioactive boron-10 (^{10}B) to produce high energy alpha particles (^{10}B [n, alpha] ^{7}Li). Meningiomas are the most common extraaxial brain tumors and are typically derived from arachnoid cells. Although the majority of meningiomas are benign (WHO grade I), some are clinically aggressive and can lead to significant morbidity and even death. High-grade meningioma (WHO grades II and III) is a difficult pathology to control, similar to high-grade glioma. Gross-total resection of skull base meningiomas (SBMs) is particularly challenging, and extended surgical resection frequently is associated with serious complications. We evaluated treatment of high-grade meningioma using BNCT.

Materials and Methods: Thirty-one patients with recurrent high-grade meningioma (7 SBMs) were treated by BNCT between June 2005 and May 2014, which was carried out in a clinical nuclear reactor research facility (Kyoto University Research Reactor Institute, Kumatori, Japan). All patients had treatment-resistant progressive meningiomas despite repetitive surgery and radiation. Fluorine-18 labeled boronophenylalanine (^{18}F-BPA) PET was performed before BNCT in 29 of the 31 cases. The clinical regimen of BNCT for malignant meningiomas was modified slightly from that for malignant gliomas. Patients were typically administered 500 mg/kg of BPA with or without 5g of BSH per person. Compound uptake, tumor shrinkage, long-term control rate including survival time, and failure patterns were evaluated.

Results: High-grade meningioma showed good boron accumulation in ^{18}F-BPA PET studies, 3.8 times higher compared with surrounding normal brain. The original tumor sizes were between 0.64cm^3 and 147cm^3. In several cases, tumor showed transient increases of volume but all lesions decreased in size during the observation period. The average depth of tumor from the skin surface was 77mm in SBMs and 51mm in non-SBMs. In BNCT, the minimum tumor doses in SBMs or non-SBMs were 24, 42 Gy-Eq, respectively. There were no differences in median survival time (MST) after BNCT (SBMs: 18.9 vs non-SBMs: 40.4 months, p=0.54) or MST after diagnosis of high-grade (SBMs: 67.5 vs non-SBMs: 47.5 months, p=0.99). Major cause of death was systemic metastasis and CSF dissemination.

Conclusion: Based on this preliminary study, BNCT may be a promising therapeutic modality for cases of high-grade SBMs. However, control of deep-seated SBMs is difficult using single dose irradiation with a reactor based neutron source. Better outcomes can be expected for BNCT using accelerator based neutron sources capable of fractionated irradiation or multiple field irradiation.

BREAKOUT SESSIONS

High-Power Liquid-Lithium Target Neutron Source Operation and Gamma Radiation Characterization

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A free surface liquid-lithium jet target is operated routinely at Soreq Applied Research Accelerator Facility (SARAF), bombarded with a ~1.92 MeV, ~1.5 mA continuous-wave narrow proton beam. Along the last two years the LiLiT was irradiated for hundreds of hours, and various aspects of the target operation and radiation were investigated. The presentation will discuss the experience gained with operation of a liquid-lithium target with a high-power ion accelerator. The experiments demonstrate the Liquid Lithium Target (LiLiT) capability to constitute a robust intense source of epithermal neutrons, for Accelerator based Boron Neutron Capture Therapy (BNCT). LiLiT generates ~3×10^{10} n/s with average energy of 30 keV, which is more than one order of magnitude larger than near threshold ^{7}Li(*p,n*)-based neutron sources using a conventional solid Li target. An additional feature of the use of a thick liquid-lithium target with a high-intensity proton beam is the relatively copious production of high-energy gamma rays, principally 17.6 MeV and 14.6 MeV (~3×10^{8} γ/s/mA and ~4×10^{8} γ/s/mA, respectively) from the radiative capture ^{7}Li(p,γ)^{8}Be* reaction, together with the dominant 478-keV gamma emission (~1.6×10^{11} gammas/mA) from inelastic proton scattering ^{7}Li(*p,p′γ*). The gamma dose must be considered in the design of a BNCT irradiation system. The LiLiT gamma dose was evaluated in separate experiments, with proton energy of ~1.82 MeV, below the neutron production threshold. The gamma dose-rate was monitored by two Geiger–Müller detectors placed on the surrounding walls. The high energy gammas were observed with a 6" × 4" NaI(Tl) detector positioned behind a 1.5 m thick concrete wall (shielding the overwhelming 478-keV). The ability to irradiate the target below the neutron production threshold was also exploited to measure the gamma dose close to the lithium flow using TLD dosimeters and various gamma activation foils, without neutron background. Another important issues in the routine operation of such a target is the activity of the residual radionuclide ^{7}Be, produced via the ^{7}Li(p,n)^{7}Be reaction, which might cause radiation risks around the system. To study the dynamics of ^{7}Be in a liquid lithium loop after high-intensity proton irradiation and to assess the produced dose rates, spectroscopic gamma-ray measurements of the ^{7}Be activity around the lithium loop were conducted. Monte-Carlo simulations of the system were compared to the measured results and good agreement was found. A cold trap was designed and built within the lithium reservoir and its potential to preferentially collect ^{7}Be was investigated. A new upgraded LiLiT system is in preliminary design stage. The upgrade will include a wider lithium nozzle and improved electro-magnetic pump to reach higher lithium velocity and improve the target beam power dissipation potential. The new target will also include a shielded and replaceable lithium container, to deal with ^{7}Be hazard.

Design and Optimization of the Beam Shaping Assembly of a Deuterium-Deuterium Neutron Generator-Based BNCT System

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Currently BNCT is performed only at nuclear reactors, which are too expensive and complex for clinical settings. Development of an alternative neutron source that is appropriate for in-hospital installation and satisfies the clinical requirements for BNCT is essential to the advancement of BNCT. A compact accelerator, such as a deuterium-deuterium (DD) neutron generator, is less expensive and easy to install and could potentially increase the availability of BNCT. The overall objective of our research is to develop and characterize a DD neutron generator-based BNCT system. Our previous study has shown that neutron energy range from 0.5eV-10keV was optimal for BNCT of deep-seated brain tumors. The purpose of this study is to design a beam shaping assembly (BSA) using computer simulations to moderate neutrons produced from a DD neutron generator from 2.45 MeV to the desired energy range.

Monte Carlo N-Particle Transport Code was used in this study. The simulation model included a DD neutron source, a BSA surrounding the source, and a head phantom. The neutron source was a planar source that was modeled according to the DD neutron generator in our lab and emitted 2.45-MeV neutrons isotropically. The BSA enclosed the neutron source and consisted of a reflector, moderator, filter, and collimator. Various types of materials, thicknesses, and geometries were tested for each BSA component to optimize the final neutron output. Evaluation criteria included in-air and in-phantom parameters. The in-air parameters were the epithermal flux (φ_{epi}), thermal-to-epithermal ratio ($\varphi_{thermal}/\varphi_{epi}$), fast neutron dose per epithermal neutron (D_f/φ_{epi}), and photon dose per epithermal neutron (D_γ/φ_{epi}). The in-phantom parameters were the advantage depth (AD), advantage ratio (AR), and advantage depth dose rate (ADDR). In addition, the maximum skin dose and the DD neutron yield that is needed to perform BNCT within one hour were calculated.

Results showed that lead was the ideal material for reflector and collimator and cadmium for thermal neutron filter. The thickness of the reflector was 30 cm and the cadmium was 0.01 cm. The collimator was 10 cm thick and created a beam aperture of 12×12 cm^2 at the exit window. The moderator was made of 45 cm of Li^7F and 10 cm of MgF_2. The in-air beam characteristics were as the following: φ_{epi} was 1.0×10^5 n_{epi}/s; D_f/φ_{epi} was 5.5×10^{-13} Gy/n_{epi}; D_γ/φ_{epi} was 2.4×10^{-13} Gy/n_{epi}, and $\varphi_{thermal}/\varphi_{epi}$ was 0.05. The AD and AR were 12.1 cm and 3.7, respectively. The ADDR was 3.2×10^{-3} cGy-Eq/min. The maximum skin dose was 0.56 Gy-Eq. To satisfy the IAEA recommendation on epithermal flux and irradiate within one hour, the DD neutron intensity would need to be 4.9×10^{13} n/s. Future works will design experimental studies to validate the simulation results and examine clinical aspects of BNCT.

Status of Accelerator Based BNCT Neutron Irradiation System using $^{7}Li(p,n)^{7}Be$ Near Threshold Reactions for Liquid Lithium Target

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The neutron irradiation system (NIS) for boron-neutron capture therapy (BNCT) should supply low-energy neutron irradiation field less than several tens of keVs and also have enough neutron intensity and temporal stability. Recently, the improvement of the accelerator technology has overcome the neutron intensity shortage using the $^{7}Li(p,n)^{7}Be$, $^{9}Be(p,n)^{9}B$, $^{9}Be(p,xn)X$ reactions. The remained subjects for Acc-based BNCT-NIS are to get the temporal stability in the practical handling.

When the research and development of Acc-based BNCT-NIS approaches its practical implementation, the technical main issues are the heat removal of 30-80 kW and for the radiation damage at the neutron producing target. Accordingly, high reliability of neutron producing target which is brought about by the safety, stability, security of the system, is required as a clinical implementation. The Acc-based BNCT-NIS using neutrons from $^{7}Li(p,n)^{7}Be$ with the liquid lithium target was already known having a good stability. The $^{7}Li(p,n)^{7}Be$ near threshold reaction combined with a liquid lithium target has an advantage for the on line dose monitoring system such as PG-SPECT system during clinical BNCT.

A stable liquid lithium jet flow was established at January 2012 for the neutron producing target of BNCT. We have focused on the combination of a liquid lithium target and a stable and high current proton accelerator such as an electric statistic type is considered as a promising candidate for BNCT.

The status of our BNCT-NIS project will be reported at the conference.

Thermal neutron source based on medical electron Linac

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The availability of a compact and easily accessible thermal neutron source is of main interest for the NCT scientific community. This contribution is focused on the design and setup of a thermal photo-neutron source based on an electron Linac Elekta Precise SL 24 MV, commonly used in hospital for radiotherapy. The machine has been installed at the Physics Department laboratory of Turin University, in collaboration with INFN (Istituto Nazionale Fisica Nucleare) and it will be entirely dedicated to scientific research with the possibility to tune its working parameters and consequently set the beam properties for radiobiology studies. Even if epithermal neutron beams are preferred for the treatment of deep tumors, a pure thermal neutron field is required when studying the effect of boron carrier compounds on cell cultures and biological samples.

The neutron production arises from (γ,n) reactions involving photons emitted by bremsstrahlung of the electron beam on a high Z target. Two ways have been investigated for the beam conversion. In the first solution the Linac internal tungsten target is used and a photo-converter is applied to the accelerator head at the gamma-beam exit; neutrons are then produced via giant dipoleresonance in a suitable lead target and then slows down to thermal energy with an appropriate moderator structure. The second possibility is to use the same target for the two reactions: in this case the converter has to be coupled to the accelerator directly at the e-beam exit. Even if the last solution can lead to a better efficiency in neutrons production, the first one has the advantage that doesn't require any modification to the original accelerator, so that it is easily reproducible on each radiotherapy Linac. Both solutions are being evaluated and are matter of discussion in this contribution.

MCNP6 code has been used for the study and the optimization of the two converters. In both cases materials and geometries have been chosen to guarantee a reasonable high quality of the thermal neutron field in the experimental cavity with respect to fast neutron and gamma contaminations. The experimental cavity is part of the photo-converter design and it can be shaped with the dimensions of the wanted application. Simulations results for the optimized

configuration show a thermal neutron field purity of about 90%, with an epithermal component of 9% and fast component of 1%. The gamma residual fluence background is reduced to less then 10% of the thermal fluence.

The final amount of thermal neutrons in the experimental cavity can be regulated by tuning the accelerator beam current. Measurements with a prototyped photo-converter are now under way in order to study the potentiality of this machine and the response of the system with different machine configurations. Accurate measurements of the neutron field purity and uniformity in the experimental cavity are also foreseen. Both passive detectors, such as bubble dosimeters, and active diagnostics are used to evaluate the thermal and fast neutron flux in the cavity. In particular, new Thermal Neutron Rate Detectors (TNRD), based on solid state devices, are under development for the installation of a permanent monitor system of the neutron field in the photo-converter.

Their properties and performances are part of the project here described and they will be discussed in this contribution.

Evaluation of relationship between uptake of L-BPA in Clear Cell Sarcoma Cell Line and L-type amino acid transporter 1

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Introduction: Clear cell sarcoma (CCS) is a rare malignant tumor with a poor prognosis. Although the standard treatment for CCS is wide surgical resection, there are no effective treatment methods. *P*-borono-L-phenylalanine (L-BPA), L-type amino acid transporter-1 (LAT-1) carries $_{L}$-BPA into tumor cells, mediating the efficacy of BNCT. Malignant melanoma cells preferentially take up $_{L}$-BPA because its chemical structure is similar to that of tyrosine, which is required for melanogenesis. CCS cells also produce melanin, making it possible for CCS cells to take up $_{L}$-BPA. Indeed, our previous study demonstrated that CCS has the ability to highly take up ^{10}B with the use of *p*-borono-L-phenylalanine (L-BPA) *in vitro* and *in vivo*. As a result, disappearance of the tumor could be achieved after BNCT was carried out for CCS- bearing mice. However, difference of antitumor effect among CCS cell lines based on an uptake amount of L-BPA was showed in these studies. Thus, BNCT utilizing $_{L}$-BPA could be a novel clinical option to treat CCS, provided that this research could reveal the mechanism of uptake. We evaluated the relationship between uptake of L-BPA in CCS cell lines and LAT-1.

Materials and methods: Four human CCS cell lines (HS-MM, KAS, MP-CCS-SY and SU-CCS-1) and two LAT-1 positive cell lines (MCF-7, a breast cancer cell line of human origin and G-361, a malignant melanoma cell line of human origin) were used. These cell lines were cultured and exposed to 8 mM BCH, an inhibitor of system L-type amino acid transporters, containing media for 10 minutes. After 10 minutes, BPA-Fr was added to this culture media to make ^{10}B concentration it 30 ppm (μg ^{10}B/mL) and exposed for 4 hours. Then the expression of LAT-1 was detected by westan-blott method.

Results: The proteins of LAT-1 and Na^+/K^+ ATPase, loading control of integral membrane protein, were observed in each cell line by westan-blott method. The uptake of ^{10}B in four CCS cell lines and control cell lines was inhibited by pretreatment with BCH. The inhibitory efficiency was 31.6 to 55.6%, each CCS cell line showed the same amount as control cell lines and may correlate with expression level. These results indicated that LAT-1 was expressed in CCS cell lines and played a key role in uptake of L-BPA.

Conclusion: The expression of LAT-1 and uptake study with an inhibitor of system LAT-1 were performed in four human CCS cell lines. This study, revel that LAT-1 was expressed in CCS cell lines and played a key role in uptake of L-BPA.

Biokinetic of BPA for liver malignancies: Preclinical, clinical and extrapolation studies.

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Introduction: In order to determine the details of BPA's bio-distribution necessary for a precise treatment planning of an extra-corporal liver BNCT partial human biokinetic models were aligned with rodent biokinetic models, the latter of which were extrapolated to the human metabolism with the help of mathematical extrapolation models.

Methods: Dynamic [^{18}F]FBPA-microPET studies of naïve mice, testing different administration routes and fasting states were performed as well as dynamic [^{18}F]FBPA-microPET studies of mice with HuH-7 cells with a subsequent measurement of extracted organs using a gamma-counter. Furthermore dynamic [^{18}F]FBPA – PET/MR scans were conducted in a rat model. Interspecies extrapolation methods to interpolate the biokinetics between both mice and rat as well as for the extrapolation to humans included the "%-kg/g" method, allometric scaling of the metabolic rate and mechanism-based PK extrapolation applied on the k_i of a two-tissue four-rate constant (2T4K) compartment model. The results were compared to compound analysis studies of analogously handled mice injected with BPA and clinical data published earlier in Mainz.

Results: The [^{18}F]FBPA – PET/MR showed an enhanced contrast in the liver 35 minutes after the injection of a MR contrast agent and 120 minutes after administration of [^{18}F]FBPA. A comparison of [^{18}F]FBPA's biokinetics in blood and liver between mice and rats shows that after an initial time of about 20 minutes the Standardized Uptake Values (SUV) of the species run parallel to each other, with the value in rat steadily being higher ~18% and ~11% for liver and blood respectively. The differences vanish completely after 50 minutes when allometric scaling is applied. When comparing the biokinetics in blood for [^{18}F]FBPA in mice, extrapolated with the "%-kg/g" - method to BPA in humans for the same administration route, lower uptake in blood is obtained for mice. Likewise the reported concertation in human tumor samples clearly ranges higher (20 -34 ppm) than the prediction from the animal studies with ~8 ppm for BPA and ~13ppm for [^{18}F]FBPA. The tumor/blood ratio however shows a perfect agreement, suggesting this quantity to be insensitive to species. For the liver uptake the "%-kg/g"- and a combination of "%-kg/g"- and mechanism-based PK extrapolation of mouse to human differ at the beginning, but align after ~70 minutes, yielding a boron concertation in of 12 -13 ppm after 120 minutes, a value which is higher than for BPA in mouse with 7.3 ± 1.3 and the human data with 9.8 ± 0.5. As a consequence the tumor/liver ratio is considerably higher in the human trials ranging from 2.6 to 3.5 whereas both animal studies extrapolated to human yield 1.1 ± 0.2.

Conclusion: All available data indicate that the tumor to liver ratio is a quantity which steadily increases and reaches saturation ~ 2 hours after start of administration. This corresponds to the optimal time point for transplantation and irradiation in an extra-corporal liver BNCT.

Electroporation enhances tumor control induced by GB-10-BNCT in the hamster cheek pouch oral cancer model

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Introduction: A critical aspect of the therapeutic efficacy of BNCT is the biodistribution of ^{10}B in tumor and in the dose limiting normal and precancerous tissues in the target volume. Given that electroporation (EP) can act as a non-specific system to administer anti- tumoral agents, the aim of the present study was to evaluate if EP could improve the targeting of ^{10}B in BNCT mediated by the boron compound GB-10, thus increasing tumor response *in vivo* in the hamster cheek pouch oral cancer model (HCPOCM). In addition, we evaluated the effect of EP post-administration of GB-10 on the mean gross boron concentration of ^{10}B in tumor, precancerous tissue and normal tissue in an attempt to understand the mechanisms involved. **Materials and methods:** Tumor bearing hamster cheek pouches (cancerized with DMBA) were treated with: 1) GB-10-BNCT without EP (n=33 tumors) and 2) GB-10-BNCT+EP (10 min. post-administration of GB-10) (n=46 tumors). Irradiations were carried out 3 hours post-administration of GB-10 in the thermal facility of the RA-3 Reactor in the Centro Atómico Ezeiza with a neutron fluence of 1.9 x 10^{12}n/cm^2. Tumor response and degree of mucositis in precancerous tissue surrounding tumors were evaluated 7, 14, 21 and 28 days post-irradiation. Fisher´s exact test was used to assess the statistical significance of the difference in tumor response between protocols (statistical significance was set at $p<0.05$). In additional groups we performed biodistribution studies of ^{10}B with 1) GB-10 without EP (n=20 tumors) and 2) GB-10+EP (n=13 tumors). Tissue samples were taken 3 hs post-administration of GB-10 and processed to measure [^{10}B] by ICP-MS. Statistical analysis of the biodistribution data was performed using unpaired t test ($p<0.05$). Experimental studies in animals were conducted in accordance with the GCULA (NIH, 1996) and CICUAL-CNEA. **Results:** We observed a statistically significant increase ($p< 0.0001$) in complete remission of tumors in protocol GB-10-BNCT+EP **(**46%) vs protocol GB-10-BNCT without EP (6%). Likewise, overall tumor control (complete remission + partial remission) increased significantly ($p< 0.0001$) in protocol GB-10-BNCT+EP (92%) vs protocol GB-10-BNCT without EP (48%). For both protocols toxicity (mucositis) in precancerous tissue was reversible and slight/moderate. Biodistribution studies showed that mean gross ^{10}B concentration in tumor in the case of GB-10+EP (20.2±9.6 ppm ^{10}B) was significantly higher ($p<0.01$) than in the case of GB-10 without EP (9.5±2.4 ppm ^{10}B). Similarly, Tumor/Normal Tissue and Tumor/Blood [^{10}B] ratios were significantly ($p< 0.01$) higher for GB-10+EP versus GB-10(2.3±0.8 vs 1.0±0.2 and 1.3±0.4 vs 0.5±0.1, respectively). **Conclusion:** Electroporation increases the therapeutic efficacy of GB-10-BNCT *in vivo* in the

HCPOCM without inducing severe mucositis in the dose-limiting precancerous tissue. Biodistribution studies suggest that EP-induced significant increase in mean gross boron concentration in tumor and in Tumor/Normal Tissue and Tumor/Blood ratios would enhance GB-10-BNCT- induced tumor response. Qualitative neutron autoradiography studies corresponding to the GB-10+EP protocol vs the GB-10 without EP protocol showed improvements in the microdistribution of ^{10}B in terms of the preferential localization of GB-10 in tumor parenchyma compared to stroma.

Therapeutic efficacy of Boron Neutron Capture Synovectomy (BNCS) mediated by GB-10 or BPA in a model of antigen-induced arthritis in rabbits: low dose radiobiological studies at RA-1 Nuclear Reactor

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Introduction: Rheumatoid arthritis is a chronic autoimmune pathology characterized by the proliferation and inflammation of the synovium. Boron Neutron Capture Synovectomy (BNCS) was proposed to treat the pathological synovium in Arthritis. Early studies were performed employing $K_2B_{12}H_{12}$ and boronated liposomes as boron carriers. While these boron compounds have advantages and disadvantages for BNCS, none of them have been approved for use in humans. In a previous biodistribution study we showed the incorporation of therapeutically useful boron concentrations to the pathological synovium in a model of antigen-induced arthritis (AIA) in rabbits, employing intra-articular administration of two boron compounds approved for their use in humans, i.e. decahydrodecaborate (GB-10) and boronophenylalanine (BPA). The possibility of using intra-articular administration protocols is an asset because it allows for boron uptake to be maximized in the target volume, while reducing the dose administered to healthy tissues not included in the target volume. The leakage of boron into the systemic blood stream is minimum, i.e. < 4 ppm as revealed by our previous biodistribution study. The aim of the present study was to perform low dose BNCS studies at the Nuclear Reactor RA-1 in the same model. **Materials and Methods**: Fifteen minutes post intra-articular administration of BPA or GB-10, neutron irradiations were performed with the thermal beam of the RA-1 Reactor at a thermal neutron flux of approximately 1.6 x 10^8 n/cm^{2}sec to the target area (knee joint) to deliver 2.4 or 3.9 Gy respectively to synovium (*BNCS-AIA*). The geometric set-up involves no body shielding. *AIA* and healthy animals not treated with BNCS were used as controls. The animals were followed clinically for 2 months. At that time biochemical, Nuclear Magnetic Resonance (NMR) and histological studies were performed. **Results:** *BNCS-AIA* animals did not show any toxic effects, swelling or pain on palpation. In *BNCS-AIA,* the post-treatment levels of TNF-alfa decreased in 4 of 6 rabbits and IFN-γ levels decreased in 5 of 6 rabbits vs pre-BNCS values. However, the difference between mean pre and post-treatment values did not reach statistical significance, conceivably because BNCS is a local treatment and a robust systemic effect might take longer to achieve. In all cases, NMR images and semi-quantitative scoring of the knee joint in *BNCS-AIA* resembled healthy animals, with no necrosis or periarticular effusion. Synovial membranes of *BNCS-AIA* were histologically similar to those of healthy animals. No contributory differences were observed between BPA- BNCS and GB-10-BNCS groups. **Conclusion:** BPA-BNCS and GB-10-BNCS, even at low doses, would be therapeutically useful for the local treatment of rheumatoid arthritis. To the best of our knowledge, this is the first study that includes a long enough follow-up with appropriate end-points to assess clinical response. The selected protocols employ BPA and GB-10, 2 of the three boron compounds approved for their use in humans (BPA, GB-10 and BSH), thus contributing to bridge the gap between research and clinical application.

A theranostic approach using Gd/B probes combined with antitumour agents to improve Boron Neutron Capture Therapy efficacy

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The combination of different therapeutic modalities is a promising option to combat tumour recurrence, in particular using protocols or/and drugs able to target the different pull of cells forming the tumour bulk. To this purpose, in this study, BNCT has been combined with two adjuvant treatments based on: i) the co-administration of curcumin: a natural molecule characterized by a strong anti-proliferative effect; ii) the use of a boron carrier molecule which acts as an inhibitor of the carbonico anhydrase (CAIX) enzyme.
In the first approach PLGA nanoparticles are exploited for the simultaneous delivery of a boron-curcumin complex (RbCur) and an amphiphilic Gd complex into tumour cells with the aim of performing Boron and Gadolinium-NCT in combination with an additional curcumin anti-proliferative effect. Furthermore, the use of Gd complexes allows the MRI assessment of the amount of B and Gd internalized by tumour cells. PLGA nanoparticles are targeted to ovarian cancer cells (IGROV-1), by including in the formulation a pegylated phospholipid functionalized with the folate moiety. NCT is performed on IGROV-1 cells internalizing 6.4 and 160 ppm of ^{10}B and ^{157}Gd, respectively.
Regarding the second approach, carboranes functionalized with sulfonamides, that recently have been proposed CAIX inhibitors will be combined with BNCT with the aim of reducing radioresistance, typically shown by hypoxic tumours. In fact, CAIX is a hypoxia-inducible enzyme that is overexpressed by cancer cells including breast and mesothelioma cells and plays an important role in tumour acid-base homeostasis by promoting cancer cell survival in hypoxic microenvironment facilitating tumour cell invasiveness and metastasis. Recently, a relationship between CA overexpression and tumour cells resistance to chemio or radio therapy has been evidenced and novel antitumour therapies based on the use of CAIX inhibitors (i.e. acetazolamide, ethoxzolamide, sulfanilamide) are under study in clinical. Furthermore, a Gd-based imaging probe has been conjugated to the inhibitor carborane cage in order to assess by MRI the amount of boron at the targeted cells to find the best neutron irradiation conditions. The efficacy of the combined therapy was evaluated on breast and mesothelioma cancer cell lines and mice models. The combination of BNCT with the two therapeutic protocols (curcumin and CAIX inhibitors) have improved the efficacy of the cure by eliminating all different pull of cells including the radioresistant clones responsible of tumour recurrence often observed after radiotherapeutic protocols.

Carborane and metallacarborane inhibitors of Carbonic Anhydrase IX, compounds with possible double action.

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We have previously identified metallacarboranes and carboranes as a promising class of specific inhibitors of HIV protease (HIV-PR) and Carbonic Anhydrase IX (CA IX) enzymes. Here we report on recent advances in the molecular design of carborane and metallacarborane inhibitors targeting CA IX isoenzyme. This enzyme, which is associated with solid hypoxic tumors, belongs to newly identified targets for cancer therapy and diagnostics.

The scope of currently available site-directed modifications on various boron cages is critically overviewed, with an emphasis on the progress in the synthesis of carboranes and metallacarboranes substituted by sulfamide, sulfonamide and other similar groups, *i.e.* functions known to bind tightly to the zinc atom in the active site of CA-IX. The new generations of polyhedral inhibitors of CA-IX, based on the careful selection of boron cages and optimized substitutions, exhibit significantly enhanced *in vitro* activities with corresponding Ki values in the range of tenths of pM to several nM. The structure-activity relationship (SAR) observed within a small library of ca. 60 substituted carboranes and metallacarboranes is discussed.

These results are complemented by some synchrotron structures of enzyme-inhibitor complexes and by a short overview of pharmacologically relevant factors such as plasma protein binding, cell membrane penetration, and basic results from toxicology and pharmacokinetic studies (mouse model) performed on a panel of the selected inhibitors of CA IX enzymes.

Due to promising inhibitory properties, these compounds are thus primarily considered as candidates for drugs applicable in cancer treatment. Nevertheless, due to their high selectivity for tumor-associated CA-IX isoform, these boron species may also offer a reasonably high potential for future use in BNCT. Indeed, the first ^{10}B labelled carborane inhibitors were already prepared in our laboratories and submitted for testing.

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Development of New Generation Drug Delivery System for Boron Neutron Capture Therapy

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BNCT is a binary therapy with selective delivery of non-radioactive 10B to cancer cells and thermal neutron beam. When 10B and thermal neutron irradiation are kept distinct, each has only a minor effect on cancer cells; albeit uniting both elements at a tumor releases intense radiation destroy malignant cells. Because the path lengths of the particles are only in the single cell range, approximately 9-10 μm, tumor containing 10B compounds are selectively destroyed by BNCT therapy. The selective tumor targeted boron delivery system is very crucial for effective treatment. Therefore, the key to make BNCT more reliable cancer therapy is the effective delivery and accumulation of boron compounds to the cancer cells, this is also the aim of this research.

The emerging bioorthogonal reactions involve two reactive functional groups are highly chemoselective and unreactive to the other functionalities present in biological systems, and proceed in water at or near neutral pH, between 25 and 37 °C, also do not involve cytotoxic reagents or byproducts. Click chemistry, which plays very important role in bioorthogonal reactions, is generally applied only when a reaction meets several defining criteria: (1) modular, (2) wide in scope, (3) high yield, and (4) producing nontoxic or inoffensive byproducts. Orthogonal reactivity and concomitant application of click reactions have become critically important to a variety of fields, and click chemistries have already been demonstrated for functionalizing various biologicals, polymeric materials, surfaces, and inorganic nanomaterials. In this research, we will apply these conjugation techniques to develop dual formulations as boron agents for BNCT, e.g., conjugation of tumor targeting functional moiety and boron compounds with tetrazine ligation. Especially, Tetrazine cycloaddition with rapid kinetics and high specificity is a powerful tool for bioorthogonal reactions, and will play major role in this research. We will synthesize several norbornenes combined with hypoxia marker, folic acid, etc. for tetrazine Diels-Alder cycloaddition. Also, we will prepare various boron functionalized tetrazines for conjugation to functionalized tetrazines. The subsequent bioevaluation will be held with synthesized tetrazine-norbornene adducts, such as cell viability and evaluation uptake of adducts in tumors. The future objective of this dual formulations strategy is not only to apply practically on BNCT, but also have route-to-market, intellectual property, and integration of biotechnology and pharmaceutical industry.

Methodology for Dosimetric Characterization of the Neutron Therapeutics Accelerator-Based BNCT System

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For development and clinical implementation of the accelerator-based neutron sources for boron neutron capture therapy (BNCT), it is of crucial importance that the characteristics of the neutron beam are determined in a coherent and reproducible way, both in air (beam geometry as well as neutron and photon spectra), and in a phantom (absorbed dose and neutron fluence distributions). Consistent dosimetry is required for reliable comparison between BNCT facilities as well as conventional radiotherapy. Basic dosimetric methods must also be traceable to the international standards.

When establishing the beam characterization methods for the Neutron Therapeutics accelerator-based BNCT System, the recommendations developed by the European BNCT research groups ("Recommendations for the Dosimetry of Boron Neutron Capture Therapy (BNCT)" published by the Nuclear Research & Consultancy Group (NRG)) will be followed.

Neutron fluence rate will be measured using activation foils. The multiple foil activation method will be used for neutron spectrum measurement. The paired ionization chamber technique will be used for the measurements of the total, fast neutron, and photon absorbed dose. The reference conditions for determination of the dosimetric quantities for beam calibration and beam model verification will be established in a water filled rectangular phantom.

A reliable beam monitoring system has been developed for beam calibration and reliable dose delivery to the patient.

Comparison between TLD-700 and TLD-100 reliability for measuring both gamma dose and thermal-neutron fluence in radiation fields for NCT

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Thermoluminescence detectors (TLDs) are frequently used in dosimetry for neutron capture therapies (NCTs). The most common choice is that of Lithium Fluoride (LiF), owing to the high cross section, for thermal neutrons, of 6Li for the reaction 6Li(n,α)3H. The thermoluminescence emissions after photon or thermal-neutron irradiation are different: the relative heights of the two main dosimetric peaks of the glow curve (GC) are consistently different. Various experiments have been carried out using LiF:Mg,Ti chips with different ratios of 6Li and 7Li isotopes: TLD-100 (containing 7.5% of 6LiF and 92.5% of 7LiF) and TLD-700 (containing 0.01% of 6LiF and 99.99% of 7LiF). In the very high neutron fluence rates of research reactor beams (108 cm-2 s-1 or higher) the low amount of 6Li in TLD-700 causes a non-negligible contribution due to thermal neutrons in their response, sometimes comparable to the gamma-dose contributions.
The proposed method for attaining both thermal-neutron fluence and gamma dose from the GC of a single TLD exploits the different ratio of the heights of the two dosimetric peaks of the GCs from the LiF:Mg,Ti detectors when irradiated in photon and thermal-neutron fields. The evaluations of thermal-neutron fluence and gamma dose are obtained with suitable algorithms containing the heights of the two dosimetric peaks. The same algorithms can be used both for TLD-700 and for TLD-100. The precision of the obtained values depends on the ratios of gamma and thermal-neutron components because it depends on the relative entities of the two contributions in the GC. If the contribution in the GC of one of the two components is small with respect to the other one, this component is evaluated with a higher error. Depending on the field configuration, one or the other field component may give a very low contribution in the measured GC and therefore it may lead to large error in the consequent evaluation. In the here considered neutron fields, in the GC of TLDs-700 the contribution due to thermal neutrons may be very low with respect to that due to the gamma dose and, on the opposite, in the GC of TLDs-100 the gamma dose may give a low contribution because of the high amount of 6LiF. The use of TLDs-700, however, is particularly convenient because such detectors do not undergo radiation damage in the high thermal-neutron fluence rates of NCT neutron sources.
A lot of measurements have been performed with TLDs-700 and TLDs-100 at the LVR-15 research reactor in various irradiation configurations and the reliability of the results obtained with TLDs-700 and TLDs-100 for thermal-neutron fluence and gamma dose were compared, in order to establish the TLD choice and analysis modality that could give consistent results.

Computational Dosimetry Comparison between External Ion Beam Therapy and BNCT

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Radiotherapy with particles that are made of quarks is usually categorized as hadron therapy. This categorization is correct if only primary radiation is concerned. When speaking of damage to tumor, proton therapy, heavy ion therapy and boron neutron capture therapy (BNCT) have different mechanisms to destroy tumors. Proton and carbon ion therapy using primary particles are basically the upgrade version of conventional external radiotherapy, as the damage to tumor is exactly from the primary particles and higher biological effects. The term external ion beam therapy (EIBT) is used in this study to describe proton and carbon ion therapy. Whereas BNCT is essentially a binary treatment modality, the damage to tumor is mostly from high LET ions produced by nuclear reaction when the neutrons are absorbed into boron-10, and not due to the primary neutrons. More practically, as BNCT combines the features of targeting molecular carrier with hadron therapy, it should be expressed as molecular targeting guided hadron therapy (MTGHT). In order to suggest a more correct explanation for BNCT, this work tries to clarify the difference between EIBT and BNCT via a computational dosimetry study. Therapeutic beams of proton, carbon ion, and accelerator-based BNCT (AB-BNCT) were created to irradiate a voxelized Snyder phantom with sole and dual tumors of tiny volume (0.144 cm^3) for comparison. The spread-out Bragg peaks of proton and carbon ion beams for irradiation were generated by a numerical model, and the neutron spectrum of AB-BNCT was obtained from lithium target. The diameter of the BNCT beam was 10 cm and was being confined to 1 cm using an extended collimator. The direction of the beams was planned as horizontally incident. The boron concentration for BNCT dose calculation was 30.0 for tumor and 10.0 for normal tissue, as well as the boron distribution in the phantom was assumed homogeneous as usual. Conventional radiation weighting factors of RBE and CBE were applied to the dose weighting procedure. This study provides discussion not only on the calculated results including percent depth dose and dose volume histogram, but also on the questioning assumptions on RBE values of the treatment modalities of interest and homogeneous boron concentration. A clear picture of the current advanced treatment modalities will be shown to reveal the most significant difference between EIBT and BNCT and to demonstrate the advantage of BNCT over EIBT.

An early inflammatory and immune cascade activation after BNCR in human cancer cells

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To understand the cellular responses after boron neutron capture reaction (BNCR) in human cancer cells, comprehensive analysis of transcriptome and proteome was carried out using oral squamous cancer SAS cell line. Cells were irradiated with thermal neutron beam at KUR nuclear reactor (Kyoto University, Osaka) at different doses with/without BPA conditions. Six and twenty-four hrs after thermal neutron beam irradiation at the dose of 24 Gy-eq in boronophenylalanine (BPA) (+) and BPA(-) conditions, cells were harvested and RNA and protein were analyzed. We observed that induction of several transcription factors including ATF3, EGR1, MAFB 6 hrs after BNCR. Inflammatory and immune cascade genes such as IL-6, IL-8, CSF2 were induced at this time point. ELISA analysis showed that CSF2 gene product (GM-CSF) level was augmented from 6 hrs in the culture supernatant after BNCR. Compared to 24 Gy γ-irradiation using 137Cs source or carbon-beam irradiation, the GM-CSF increase in the culture supernatant occurred earlier in BNCR. In melanoma A375 cells, augmentation of GM-CSF in the culture supernatant was also observed earlier and at a higher level after BNCR compared to γ-irradiation. The results suggest that the early increase of GM-CSF could be involved in the microenvironmental or systemic responses for BNCR.

CBE factors for boron compounds to the tumor varies depending on their ^{10}B levels – radiobiological consideration about its significance –

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A fixed value of CBE (compound biological effectiveness) factors for boron compounds has been generally used to the tumor dose in clinical BNCT. In order to examine the right or wrong, our reported data were reanalyzed. In their reports, the effects of BNCT to tumor cells were examined by *in vivo in vitro* colony formation assay. And the relation was determined between surviving cell fraction (SF) of tumor (SCCVII) cells and neutron fluence (ϕ). It was possible to describe the relations in every test group by an equation of $SF=C \cdot e^{-\alpha\phi}$. C ranged from 0.99 to 1.1. In order to find the net biological effect of $^{10}B(n,\alpha)^{7}li$ reaction, $\alpha(N)$ for neutron beam irradiation alone was deducted from $\alpha(B+N)$ for the combination of neutron beam and boron compound. $\alpha(B)$ that was determined by an above manipulation increased with ^{10}B level in the tumor. The ^{10}B level was measured by prompt gamma-ray analysis. Based on the ^{10}B level and $\alpha(B)$, D_0 was calculated. The linear part of dose vs. tumor cell survival curve was also described as $SF=C \cdot e^{-D/D_0}$ following gamma-ray irradiation like as neutron beam irradiation curves. C and D_0 were 1.98 and 4.46 Gy, respectively. By comparing these D_0 values, the CBE factors for boron compounds were determined. CBE factor for BPA (l-*para*boronophenylalanine) was 5.7 at 11 ppm and rapidly decreased to 2.3 at 25 ppm. While on the other hand, CBE factor for BSH (mercaptoundecahydrododecaborate disodium) quite slightly decreased from 2.8 to 2.3 in the same range of ^{10}B level. It is thought that larger CBE factor for BPA compared with that for BSH is because of the accumulation capability of BPA into tumor cells. If the micro-distribution of boron compounds is homogeneous, the CBE factors would be independent from the ^{10}B level. Therefore, the remarkable dependency of CBE factor for BPA on ^{10}B level is attributable to the uneven micro-distribution in the tumors. Inversely, the dependency of CBE factor for BSH was minimal on ^{10}B level. This means that the more homogeneous distribution of BSH is achievable in the tumor. At high ^{10}B levels, CBE factor for BPA approached to that for BSH. This may mean that ^{10}B level of BPA in the tumor cells already reached the plateau at high ^{10}B level and the tumor cell populations with lower ^{10}B level became predominant. To clarify this point, α-ARG (autoradiography) study is indispensable.

As above, in clinical BNCT there exist many problems on the use of a fixed value of CBE factor for BPA because of its uneven micro-distribution in the tumors.

Biodistribution and convection-enhanced delivery of the boronated porphyrin in the F98 intracerebral rat glioma model

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Introduction: Boronated porphyrins and their derivatives, in particular proto-porphyrin bearing polyhedral borane anions have emerged as promising dual sensitizers for use in both photodynamic therapy (PDT) and boron neutron capture therapy (BNCT), by virtue of their known tumor affinity, low cytotoxicity in dark conditions, and easy synthesis with high boron content. The chemical composition consists of a water-soluble sodium salt of the amide (bis (tetramethylammonium) proto-porphyrin IX (PpIX) monoamide undecahydro-closo- dodecaborate (BNH2-conjugated PpIX; BNH2-PpIX).

Materials and Methods: To evaluate the applicability of BNH2-PpIX, in BNCT, we performed an in vivo study using a F98 rat glioma-bearing brain tumor model. Local infusion of BNH2-PpIX was performed directly into the brain via convection-enhanced delivery (CED). Infusion of BNH2-PpIX in the tumors was administered at doses ranging from 0.125mg to 0.5mg/200μL 24-hour period. After completion of infusion, rats were euthanized at different time points (3, 24, 48 hours after termination of CED). Samples were obtained from their blood, tumor, ipsilateral brain, contralateral normal brain, liver, spleen, kidney, skin, muscle, heart, and lung tissues. Tissues were removed for boron determination by inductively coupled plasma - atomic emission spectrometry (ICP-AES) for biodistribution study.

Results: CED of 0.25mf/200μL of BNH2-PpIX yielded an average tumor boron level of 20.2±8.1μg/g and a tumor/blood ratio of approximately 151:1 even 24 hours after CED. In addition, tumor to ipsilateral brain ratios were approximately 20:1, and tumor/contralateral brain ratios were approximately 30:1. Despite the high boron levels in tumor and in ipsilateral brain, none of the rats displayed any functional neurologic deficits or systemic complications after BNH2-PpIX infusion, and boron concentrations in the systemic organs including blood, livers and spleens in all animals were near baseline levels after CED of BNH2-PpIX at doses of ranging from 0.125-0.5mg. These results demonstrate that CED is a remarkably effective method for selective delivery of BNH2-PpIX into intracerebral brain tumors.

Conclusions: We showed that the novel boronated porphyrin, BNH2-PpIX, was an effective sensitizing agent in BNCT. The results of this CED study clearly demonstrate that this model using local delivery of BNH2-PpIX significantly enhances tumor uptake of boron. The boron levels obtained in the tumors were more than what is generally considered optimal for BNCT. Maintaining high intra-tumor boron levels even 24 hours after CED suggests the possibility of an expanded way for irradiating neutron beams in brain tumors.

Approaches to the Synthesis of Boronic Acid-Derived Sugars

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The Boron Neutron Capture Therapy (BNCT) is a binary targeted therapy, based on the neutron capture by nuclei of 10-B selectively delivered to tumor cells, that is effective for therapy-resistant tumors, leaving the surrounding normal tissues intact.
Within the context of BNCT, there are two main goals to achieve for improving its exploitability and acceptance:
1. New neutron sources, cheaper and more acceptable by the public than nuclear reactors. Today, accelerators with therapeutic neutron flux begin to be available at hospitals in Japan.
2. New and more selective agents, more specific and effective against tumor cells.
The availability of more acceptable neutron sources will certainly stimulate the research towards new BNCT agents. The generation of new compounds was seen as urgently needed even many years ago. Prof. A. H. Soloway, one of the few chemists to have brought a boron compound (BSH) into clinical use, stated: "Tumor-targeting will become less an art and more a science as we acquire a greater understanding of the biochemical and physiological differences between tumor cells and their normal counterparts and how to use these differences in compound design, synthesis, and targeting" (Soloway et al., 1998, Chem. Rev., 98, 1515-1562). On the other hand, the development of new compounds or new targeted vector systems is not easy to achieve for at least three reasons: first of all, the need of specific knowledge in boron chemistry, that usually is not present in pharmaceutical companies or in research institutes: second, the absence of intrinsic anticancer activity of compounds suitable for BNCT; third, conventional drug-testing systems and drug-development strategies cannot be applied or directly transferred into this context.
We decided to focus our recent research on the synthesis of new sugar-derived structures, containing 10-B atoms in different forms, and on their incorporation in delivery systems (nanovehicles) for selective tumour targeting.
In particular, we focused our attention on sugar derivatives containing a boronic acid in their skeleton structure. Quite surprisingly, among the multifarious carbohydrate analogs described in the literature (C-glycosides, azasugars, carbasugars, phosphonates, phostones) only few examples of derivatives where a carbon or oxygen atom is replaced by a boron atom have been reported.
We therefore concentrate our efforts on the planning and execution of reasonable synthetic schemes of the previously mentioned analogs, to get information on their feasibility, on the stability of this new class of sugar analogs and on their ability to mimic the corresponding natural sugars *in vivo*.
We will show here our initial results on different approaches to the synthesis of some of these analogs, highlighting advantages and drawbacks. If available we will also discuss preliminary biological data on toxicity and biodistribution.

Hypoxia Targeted Boron Delivery Agent for BNCT Treatment of Brain Tumor

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Brain tumors pose a particular challenge in cancer treatment because of the additional hurdle imposed by the blood-brain barrier, which effectively excludes most chemotherapeutics from the brain. Surgery is often limited by the inaccessibility of the tumor location. Radiation therapy is therefore the default treatment modality, but its efficacy is limited by the fact that gliomas tend to be highly hypoxic, with hypoxic tumor cells comprising more than 50% of the tumor mass, and hypoxic cells are particularly resistant to radiation therapy. Therefore, there is a critical need for a more effective treatment. Boron neutron capture therapy (BNCT) is an unique method in that the radiation dose is delivered internally when tissue containing boron atoms is irradiated with neutrons. When boron atoms capture a neutron they immediately undergo fission to produce a lithium atom and an alpha particle, which destroys the tumor cell. Because neutrons by themselves have relatively little effect on tissue, BNCT offers the possibility of delivering a very high radiation dose very selectively to the tumor without significant damage to surrounding tissue, a particular concern in the brain. The primary limitation of BNCT has been the absence of a boron-rich compound that selectively accumulates in tumors. Boronophenylalanine (BPA) is the only approved boron delivery agent, and it is far from ideal. The objective of our study is to develop a novel theranostic agent for both the identification of hypoxic regions in brain tumors and the treatment of these tumors by BNCT. Recently we synthesized the hypoxia-targeted boron delivery compound NPI-BNCT-001B and demonstrated that it provides an exceptionally high glioma-to-normal-brain tissue ratio of 8:1 and 4:1 in tumor bearing F98 rats and ALTS1C1 mice, respectively. Boron concentration in brain tumor was measured at 43 μg/g in the mice. They received neutron radiation (1.2 MW, 15 min) with or without 2 X 3 mg of NPI-BNCT-001B i.p. at 16 days after tumor inoculation. NPI-BNCT-001B produced extension of survival to 41 days vs. 25 days for controls. NPI-BNCT-001B is a novel molecule that combines a nitroimidazole moiety for targeting hypoxia, a B10 cluster for BNCT, and an additional arm that can be radiolabeled with ^{18}F for PET imaging to validate delivery of the compound to the tumor and to guide delivery of the neutron beam to the boron-enriched tumor site.

Boramino Acid: A New Theranostic Platform Serves Imaging Guided Boron Neutron Capture Therapy

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OBJECTIVE

A new class of amino acid mimics—boramino acids (BAAs)—are described here that can serve as theranostic boron delivery agents for imaging guided BNCT cancer treatment. The structure of a BAA is identical to that of the corresponding natural amino acid, except for an exotic replacement of the carboxylate with trifluoroborate. Cellular studies demonstrate the cell uptake of BAA is strongly mediated to amino acid transporter, of which the abnormal expression is often associated with cancer. In addition, animal studies of F18 labeled BAA (^{18}F-BAA) show high tumor-specific accumulation with PET (positron emission tomography), suggesting that BAA holds great promise for the development of new PET imaging probes and AAT-targeting boron agents for BNCT cancer therapy.

METHOD

A boron-derived Leu (B-Leu) derivative was synthesized to mimic Leu, of which the transportation depends on L-type amino acid transporter (LAT). ^{18}F-^{19}F isotope exchange reaction was conducted for radiolabeling and quality control was performed by both HPLC and radioTLC. The metabolic stability of B-Leu was assessed both *in vitro* and *in vivo*. PET imaging were performed in mice bearing UM22B xenografts, and ^{18}F-B-Leu is co-injected with 10 mg of unlabeled boron-derived Leu. The animals are sacrificed right after PET scan, and organs are collected for ICP analysis.

RESULT

At 60 min post injection, ^{18}F-B-Leu shows high accumulation in UM22B tumor (11.9 ± 2.7%ID/g) but demonstrates low uptake in the rest of the body (liver, 2.41 ± 0.36 %ID/g; muscle, 1.98 ± 0.54 %ID/g; brain, 0.35 ± 0.13 %ID/g and blood, 1.19 ± 0.47%ID/g). The tracer had predominant renal clearance but with low kidney retention. The following ICP analysis is correlated with PET imaging and shows high boron accumulation in tumor (66.7 ± 11.5 ppm) with good selectivity on healthy tissues (liver, 13.5 ± 2.1 ppm; muscle, 12.1 ± 1.9 ppm; brain, 5.9 ± 1.3 ppm and blood, 7.8 ± 2.0 ppm).

CONCLUSION

A boron-derived Leu derivative was developed and evaluated for PET-guided BNCT treatment. Administration of ^{18}F-B-Leu allowed for clear visualization of tumor xenografts, and also delivers high concentration of boron atoms into tumor that can be promising for BNCT treatment.

Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the assessment of radiation treatment in patients with re-recurrence head and neck squamous cell carcinoma

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INTRODUCTION:

Here we demonstrate an anti-tumor effect in head and neck cancer and a response rate that can be assessed with fluoride labeled boronoalanine positron emission tomography (FBPA-PET).

MATERIALS and METHODS:

FBPA-PET images were obtained from 10 histologically verified re-recurrence head and neck squamous cell carcinoma cases. The tumor/normal (T/N) ratio compared the FBPA accumulation rate for the tumor with that in the left ventricle. The intra-tumoral maximum FBPA accumulation rate was Tmax/N and the minimum FBPA accumulation rate was Tmin/N.

RESULTS:

The Tmax/N and Tmin/N ratios for these groups were 3.35(2.5-5.0) and 2.25(1.2-3.5), respectively. In all cases the Tmax/N ratios were 2.5 or more. The effective rate was as follows: complete remission (CR) in 5 cases, partial remission (PR) in 3 cases, and no change (NC) in 2 cases. The five patients with a Tmin/N ratio of 2.3 or more were in CR. As for the value of the Tmax/N ratio, the effect of treatment did not have an association. The two cases where the neutron flux was insufficient were NC. The post-radiation course of the 10 cases was as follows: 4 cases showed recurrence in the field, 3 cases showed distant metastases, 1 case showed outside radiation field of the recurrence, and 2 cases died from other factors. The median survival time of all cases was 10.5 months.

CONCLUSION:

Our results validate the efficacy of BNCT in the treatment of patients with re-recurrent head and neck squamous cell carcinoma. The T/N ratios of FBPA-PET can assess the effect of BNCT treatment. This study showed that the Tmin/N ratio may be predictive of BNCT treatment effect more closely, and in cases with poor neutron flux, the treatment response may be low. We believe that head and neck tumors are suitable for BNCT and that these results may have an impact on patient care in the near future.

Personalised BNCT?

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By directing innovative therapeutic strategies, like BNCT, to those patients that are more likely to benefit from them, i.e. by personalizing the therapy, treatment of glioblastoma multiforme (GBM) disease may be improved. For boronophenylalanine (BPA)-based BNCT, one characteristic that can be used to identify responsive patients is the expression status of the large amino acid trasporter-1 (LAT-1) molecule, a membrane-bound transport protein unit that is largely responsible for the cellular uptake of BPA - one of only 2 drugs used clinically in BNCT- and whose expression appears to correlate with boron uptake. Furthermore, it is readily detectable and corresponds to disease state. Pragmatically, in a typical treatment scenario where BNCT is administered as an alternative to photon therapy after debulking surgery it is the *residual* disease left behind that will be targeted. This requires that the LAT- 1 expression status of the brain-around-tumour (BAT) region be known, and this can be ascertained by sampling the BAT region at the time of initial surgery.

The functional LAT-1 transporter protein molecule consists of a membrane-spanning heterodimer of a specificity-determining, substrate transporting, light chain (LAT-1) and a light chain-recognising, location-determining, heavy chain (CD98/4F2hc). Here, we sought to determine the feasibility of using an immunohistochemical method to examine LAT-1 expression in order eventually to stratify GBM patients for BPA-BNCT according to likely clinical response. A panel of commercially available LAT-1 and CD98hc antibodies was thus screened for specificity on positive and negative human test tissue. Only 1 out of 9 LAT-1 and 1 out of 4 CD98hc antibodies screened were deemed suitable for the purpose. The specificity of staining was confirmed by a double-labelling procedure using both antibodies simultaneously. The LAT-1 antibody was then used for the staining of GBM-related BAT tissue samples.

Using an image analysis system (Imstar, France) the immunohistochemical expression of LAT-1 staining was quantified in terms of cell density (cells/unit area), extent (% stained cells) and intensity (optical density [OD] units). Preliminary results show the following ranges in measured variables: cell density $4.2x10^3$ -$12.3x10^3$ cells mm^{-2}; LAT expression 6%- 37%; and O.D. LAT expression 0.96-1.21 units.

These results point to a large variability in residual disease topography, similarly to that observed in corresponding tumours, and offer the potential for personalised therapy.

A case of boron neutron capture therapy for recurrent oral cavity cancer

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Introduction
There are few radical treatment for recurrent oral cavity cancer after treated with surgery and chemoradiotherapy. We performed Boron Neutron Capture Therapy (BNCT) which is tumor-cell-specific radiation therapy and obtained favorable results.

Case
A man in his twenties was diagnosed with tongue cancer at margin edge (squamous cell carcinoma, T2N0M0). Concurrent neoadjuvant chemoradiotherapy was applied with TS-1 and external beam radiation with a total dose of 40 Gy in 20 fractions of 2 Gy. 1 month after the neoadjuvant chemoradiotherapy, radical dissection with excision of the main tumor, supraomohyoid neck dissection and reconstruction using the rectus abdominis was performed. 4 months after the surgery, recurrence of masticatory muscles gap and retropharyngeal lymph node was diagnosed with biopsy and FDG-PET. BNCT was selected because of difficulty with radical radiation therapy for history of irradiation of 40Gy as preoperative chemoradiotherapy. We delivered BNCT with the tumor dose calculated ranged from 16.0 to 43.0 Gy equivalent and the minimum dose delivered to 90% of the gross tumor volume of more than 20Gy-equivalent. Recurrent lesion reduced obviously after BNCT. FDG-PET taken 3 months after the treatment showed no uptake in the lesion. Although recurrence was found in contralateral cervical lymphnode outside of an irradiation field, there was no local recurrence 21 months after the treatment with BNCT.

Conclusion
5-year overall survival for recurrent oral cavity cancer treated with chemoradiotherapy was less than 5%. This case showed that BNCT had high antitumor effect compared to standard treatment for recurrent oral cavity cancer which is chemoradiotherapy. It was expected that BNCT would be effective for patients with few curable treatments and extending survival for recurrent oral cavity cancer.

Boron neutron capture therapy (BNCT) combined with image-guided intensity modulated radiotherapy (IG-IMRT) for locally recurrent head and neck cancer: a preliminary report

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Introduction

To report the preliminary results of boron neutron capture therapy (BNCT) combined with image-guided intensity modulated radiotherapy (IG-IMRT) for treatment of recurrent Head & Neck cancer after photon radiotherapy.

Materials and Methods

BNCT was performed with boronophenylalanine (BPA)-fructose (500 mg/kg) injected intravenously in 2 phases. IG-IMRT was scheduled at 28-day interval from BNCT. Before BNCT, BPA-PET scan was done to determine the Tumor/Normal tissue (T/N) ratio for each tumor. THORplan and Velocity® were the treatment planning systems. Dose volume histogram (DVH) was generated for each modality. Prescription dose (or D80) for BNCT was intended to cover 80% of Gross Tumor Volume by DVH while limiting mucosa volume receiving > 10 Gy (Eq) as low as possible. Repeated CT simulation was done before IG-IMRT. GTV was recontoured while CTV and PTV were generated consequently with adequate margins. The dose/fractionation for PTV in IG-IMRT was 45 Gy/ 25 fractions. Tumor response criteria was RECIST (Response Evaluation Criteria in Solid Tumors) criteria v1.1. The adverse effects were graded with the National Cancer Institute common toxicity grading v3.0.

Results

From 2014 to 2016, six patients (M/F=5/1, median age 60.5 Y/O) were enrolled for this phase I/II clinical trial. Primary sites included oral cavity (N=4), mandible (N=1) and parotid gland (N=1). Previous accumulated RT dose ranged from 60 to 102 Gy. Six cases received BNCT while five completed combined treatment. The median T/N ratio was 3.3 while the median D80 was 18.9 Gy (Eq). The median interval between BNCT and IG-IMRT was 27 days. The median dose for IG-IMRT was 45 Gy. One patient had complete response and 2 had partial response. For acute toxicity, grade 1 or 2 mucositis/dermatitis were seen in all participants. Two cases had grade 3 infection or tumor pain and one had grade 4 hemorrhage. All tumor progression occurred within or near the combined irradiation fields. Three patients were alive at the time of this analysis and one remained disease-free 11 months after combined treatment.

Conclusion

Though our case number was small and follow-up time was not long enough, the toxicity of this combined treatment seemed to be similar to the previous 2-fraction BNCT. Some participants did have good response though local progression was common. Enrolment of more patients and longer follow-up are needed to make more solid conclusion.

Clinical application of the photon iso-effective dose concept in BNCT from dose-response assessments in an in-vivo oral cancer model.

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The severity of biological damage following irradiation depends on the radiation type. Therefore, equal values of absorbed dose of different radiations do not necessarily lead to the same level of biological damage. The dosimetry of BNCT comprises contributions from different types of radiation. Thus, a quantity different from absorbed dose is desirable to explain the effects observed in the clinic of BNCT in terms of outcome with photon radiation. This issue was initially discussed by González and Santa Cruz [Rad Res 178(6): 609-621, 2012] who reported that the standard procedure for computing photon-equivalent doses in BNCT showed inconsistency, which in practice leads to unrealistically high tumor doses. A more suitable approach was then introduced that defines the photon iso-effective dose as the reference dose that produces **the same level of cell survival** as a given combination of the absorbed dose components of a mixed field BNCT radiation. This approach included first-order repair of sublethal damage and synergistic interactions between the different radiations exploiting the information obtained from cell survival experiments. In the light of this formalism, the clinical outcome of the treatment of cutaneous melanoma in Argentina was assessed against the doses derived from both approaches. It followed that the standard approach is unsuitable to explain the observed outcome, while the number of controlled tumors predicted by the new formalism is statistically consistent with the observed results.

In both animal tumor models and in humans, local control and the response of dose-limiting normal tissue are commonly assessed to evaluate the success of a radiation treatment. The photon iso-effective dose formalism has been extended, redefining the photon iso-effective dose as the dose that produces **the same tumor control** as a given combination of the absorbed dose components of BNCT. This new formalism has, for the first time, allowed the determination of the photon iso-effective dose for unacceptable **complications in the dose-limiting normal tissue**. The parameters of the photon iso-effective dose model were determined for tumor and precancerous tissues from dose-response assessments carried out in the in-vivo oral cancer model of the hamster cheek pouch. For this, suitable expressions of the dose limiting Normal Tissue Complication Probability (NTCP) and Tumor Control Probability (TCP) for the reference radiation and for the mixed field BNCT radiation were developed. Based on these probability models, the tumor response and precancerous tissue (dose-limiting tissue) toxicity curves for the photon reference

radiation, neutrons alone, and neutrons in the presence of the boron compound BPA-F, were obtained and analyzed.

The hamster cheek pouch oral cancer model has been extensively used as a surrogate model for human oral cancers. Thus, the formalism introduced and the parameters derived from this animal model were applied retrospectively to evaluate the photon iso-effective dose for two head and neck patients treated in the BNCT clinical trial carried out in Finland. The observed outcomes in patients were assessed against the doses derived from the standard procedure and the proposed approach to compute photon equivalent doses in BNCT, and compared against results from photon radiation therapy.

The prospective of BNCT Project at Tehran Research Reactor

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Tehran Research Reactor (TRR) is the only active neutron source which can be used for BNCT research in Iran. TRR is a 5 MW, pool type research reactor. Its fuel assemblies contain low enriched uranium fuel plates in the form of U3O8Al alloy. Investigations show that TRR has a very good potential to facilitate for clinical BNCT applications. On the other hand, the reactor building has the required infrastructures for the purposes. This work presents the prospective of BNCT at TRR. There are two different approaches to use TRR for BNCT: 1) use the constructed thermal BNCT beam for the biological studies; 2) design and construct a new epithermal BNCT beam for the clinical trials. In case of the first approach, the following activities have been defined: in-phantom dosimetry using the constructed head phantom; design and construction of a biological sample holder and an automatic; design and construction of a system to measure the boron concentration in a blood sample; design and construction of an irradiation room at the thermal BNCT beam exit for animal treatment; gaining some experience in different related fields. In case of the second approach, there are three choices to construct an epithermal neutron beam suitable for brain tumors: 1) remove all graphite blocks from the thermal column using a robotic system and replace them with the designed filter/moderator assembly; 2) using an array of TRR spent fuel plates to construct a fission converter-based neutron beam; 3) design and construction of the beam based on the use of the medical room. Technical aspects recommend us that the medical room is the best choice which could provide an appropriate practical epithermal beam but there are some major challenges to use this facility: 1) It needs to operate the reactor core at the open pool position; 2) an in-pool beam tube should be designed, constructed and inserted between the core and the medical room wall; 3) two stainless steel plates that sealed the wall hole should be opened and all concrete blocks should be removed from the hole. These tasks are under investigation. After achieving the clinical epithermal beam and the boron concentration measuring system, the next steps will be carried out.

Computational analysis of the feasibility of treating head and neck cancer with BNCT at the RA-6 Reactor

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Between October 2003 and June 2007, 7 patients with subcutaneous nodular melanoma of the limbs were treated using the mixed thermal-epithermal neutron beam of the RA-6 Reactor (Centro Atómico Bariloche), Argentina. Thereafter, the so-called hyperthermal neutron beam B1, especially tailored for the treatment of superficial lesions, was modified both to improve the spectral characteristics of the beam and integrate a protruding conical irradiation port that optimizes options for patient positioning.

Patient recruitment to continue Phase II CNEA-Roffo clinical trial for the treatment of malignant melanoma with BNCT at RA-6 recommenced in June 2015. Since then, one melanoma patient received a single-fraction BNCT treatment using the new beam B2. This beam is composed of a mixture of thermal and epithermal neutrons and provides a thermal neutron flux peak in tissue of 1.0×10^9 n cm^{-2} s at ~1 cm, deeper than for B1.

Computational dosimetry studies carried out retrospectively in melanoma patients that received BNCT before the reactor reconversion showed that the current RA-6 BNCT facility would offer considerable advantages, in particular from the dosimetric point of view. Although B2 was originally designed for the treatment of superficial lesions, its applicability could be extended to deeper-seated targets using suitable planning strategies.

The successful clinical outcome reported by clinical groups from Finland, Japan and Taiwan in the treatment of head and neck cancer with BNCT, together with CNEA experience in experimental studies of BNCT for oral cancer prompted the investigation of the feasibility of treating head and neck cancer in humans at RA-6. As part of these studies, a pre-clinical protocol to treat dogs and cats with spontaneous head and neck tumors with BPA-based BNCT was designed.

In 2015, a terminal dog with a large nasal carcinoma was evaluated as candidate to receive treatment within the head and neck pre-clinical protocol of BPA-BNCT. Several computational simulations including different beam size delimiters and beam directions were assessed before treatment. The treatment planning was also performed taking into account the benefits reported in the small animal oral cancer model and in clinical trials by delivering two BNCT fractions a few weeks apart. As a result of the dosimetry assessments, two portals without beam delimiters

per each BNCT fraction were considered as the optimal set up to achieve a potentially therapeutic dose over the tumor, sparing the surrounding normal tissues. Between July and August 2015, the dog received the BNCT treatment as planned. The promising clinical results obtained in this first patient lead to the computational analysis in human patients.

Head and neck clinical cases successfully treated in Finland with BNCT were selected to perform computational simulations under the treatment conditions of the RA-6 BNCT facility. Dosimetry results were compared with patient reports. The set of computational tools used in this analysis brought together innovative developments in BNCT dosimetry. With the photon iso- effective dose formalism a suitable tumor control probability model as figure of merit was introduced. The predicted tumor control derived from the computational simulations was assessed against the observed clinical response.

Boron Neutron Capture Therapy for Extensive Scalp Lesions: Treatment Planning Study

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Angiosarcoma and Bowen's disease (squamous cell carcinoma in situ) are rare malignant tumors, which frequently occur in the face and scalp. Due to the wide extension of the lesions and from a cosmetic viewpoint, radiotherapy is adapted in many cases. In the treatment of extensive scalp lesions for these malignancies, the planning target volume (PTV) is defined as the whole scalp. However, there is technical difficulty to deliver a homogeneous dose to such a spherical PTV. As brachytherapy is one of treatment options for scalp angiosarcoma, laborious preparation and complicated dose calculation are needed.

Boron neutron capture therapy (BNCT) has potential applicability to treatment of multiple and disseminated lesions such as malignant pleural mesothelioma, and can also be effective for the extensive scalp lesions. Because of the large therapeutic gain, BNCT has possibility to lessen adverse effects on normal skins such as radiation dermatitis even for a whole-scalp PTV including malignant lesions and normal skin. The objective of this study is to optimize a newly- designed treatment applicator to deliver thermal neutrons homogeneously to the whole-scalp PTV.

The Simulation Environment for Radiotherapy Applications (SERA), which has been used as a treatment planning system in BNCT clinical studies, was used. The images of head CT were loaded in this system. The thermal neutron beam from the Heavy Water Neutron Irradiation Facility of Kyoto University Reactor (KUR) with collimator aperture of 25-cm diameter was applied as a neutron source. The upper part of scalp above the ears was defined as PTV. The applicator consists of two devices; a lithium-fluoride (LiF) neutron intensity modulator on the beam-incident side and a carbon neutron reflector around the head. The thicknesses of these two devices were optimized. To investigate the homogeneity of the thermal neutron distribution in the PTV, a homogeneity index (F_{90}/F_{10}) was estimated, where F_{90} and F_{10} are the thermal neutron fluences delivered in 90 and 10 vol. % of the PTV, respectively.

The values of F_{90}/F_{10} were almost the same (0.26-0.27) for the carbon neutron reflector thickness in the range from 6 to 24 cm. Then, the 6-cm-thick reflector was adapted for optimization of the thickness of the LiF neutron intensity modulator. The value of F_{90}/F_{10} was approximately 0.4 for the modulator thickness in the range from 26 to 36 mm using the 6-cm-thick reflector.

In the treatment planning study on BNCT for extensive scalp lesions, the optimized newly-designed treatment applicator consisting of the LiF neutron intensity modulator and the carbon neutron reflector can yield more homogeneous thermal neutron distribution in the whole scalp PTV in comparison with that without the treatment applicator.

Application of carbon nanohorn containing boron to BNCT

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Carbon nanohorn (CNH) is horn-shaped sheath aggregate of graphene sheets. CNH can be a candidate of drug delivering. We use CNH as a boron delivery system, Boron source was BNC_2 and these are encapsulated in the CNH. The surface of the CNH or Boron-capsulated-CNH were coated with polyethylene glycol with or without folic acid. (CNH, CNH-FA, BN-CNH, BN-CNH-FA)

To evaluate these four nanoparticles, because there was no neutron source for experiment in Japan in 2015, we use the accelerator based neutron source of Budker institute of Nuclear Physics (Novosibirsk, Russia). Due to export controls, all boron agents were made of natural isotopic composition.

V79 and U251 cell line were used. Cell medium were adjusted 40μg Boron-10/mL for boron BN-CNH, same concentration were used for CNH. After 24hrs exposure, cells were suspended and samples were irradiated neutron with tandem accelerator of Budker institute of Nuclear Physics. Because the thermal neutron dose was not equal to previous Japanese reactors, and the methods of calculations are also different, boric acid were used as a control. The colony forming assay were performed, survival rate was compared with controls.

Micro-PIXE/PIGE analysis was performed at Takasaki Ion Accelerators for Advanced Radiation Application (TIARA, Takasaki, Japan). The cellular samples with same condition that attached on thin polycarbonate membranes were freeze-dried. Elements (Potassium, Phosphate, Boron) distribution images were analyzed using MATLAB, and calculate intra cellular area boron concentration / extra cellular area boron concentration ratio.

Survival rate of 40μg Boron-10/mL of boric acid was 0.09 for U251 and 0.19 for V79. The survival rate of CNHs has showed no difference between controls. BN-CNH showed 0.23 for U251, 0.52 for V79, BN-CHN-FA showed 0.42 for U251 and 0.51 for V79.

Though these data were incomplete, but with U251 human glioma cell lines, the intra /extra B ratio reached about 2 with carbon nanotubes, and 1 with boric acid.

Though beam dose was not well established, boric acid would be useful for control. BN-CNH revealed neutron effect at least, further investigation will have needed.

Neutron irradiation of human glioma cultured cells using accelerator based neutron source.

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A modernized source of epithermal neutrons based on a tandem accelerator at BINP was used to irradiate boronophenylalanine (BPA) treated human glioma cells U251 and T98G and chinese hamster cells CHO-K1 and V79. The boron concentrations in the cell samples were measured with inductively coupled plasma atomic emission spectroscopy. Acceptable cellular uptake levels of BPA were observed. The survival of cells was analyzed after irradiation using different neutron fluencies at the same boron concentration (40 ppm) in the growing medium prior the irradiation. In cells pretreated with BPA, colony forming capacity was shown to be inhibited compared with BPA-free cells. Surviving ratios were significantly decreased in a dose-dependent manner in these cell lines, but U251cells were suppressed more strongly than other cells. Our results show that the neutron beam generated by accelerator-based source decreases significantly the viability of tumor cells pretreated with ^{10}B *in vitro*.

Boron delivery system using boronated polyethylene-glycol binding BSA for boron neutron capture therapy *in vitro*

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Cell destruction in boron neutron capture therapy (BNCT) is due to the nuclear reaction between ^{10}B and thermal neutrons to release alpha-particles (^{4}He). It is theoretically possible to kill tumor cells without affecting adjacent healthy tissues, if ^{10}B-compounds could be selectively delivered.

Recently, polyethylene-glycol(PEG) have attracted attention to escape the uptake by reticuro-endotherial systems(RES), and to accumulate into the tumor cells. PEG has been covalently linked to many different proteins, after which an increased half-life and a reduction in immunogenicity has been reported. Thus, PEG modified proteins have been applied to drug delivery systems. It have reported that inclusion of amphipathic PEG 5000 in the lipid composition effectively reduces uptake by the RES and results in prolonged circulation time of liposomes. In this study, we prepared boronated PEG-binding bovine serum albumin(BSA), and examined the delivering capacity of boronated PEG-BSA to carry ^{10}B atoms to human pancreatic cancer cell line, AsPC-1, in *in vitro*.

We prepared boronated PEG-BSA. PEG binding BSA was prepared by the method of Abuchowski et al. which was originally developed for the chemical modification of BSA. This method is based on a single step covalent binding of activated PEG to an amino group, in our case of also BSA. The delivering capacity of boronated PEG-BSA to carry ^{10}B atoms to human pancreatic cancer cell line, AsPC-1, was examined, in *in vitro*. Prompt gamma-ray spectrometry showed that 250.0±4.9 ppm ^{10}B atoms was found to conjugate to PEG-BSA. AsPC-1 cells were incubated in 250 ppm of soluble ^{10}B-PEG-BSA. The cells were washed at various times indicated and analyzed for boron content by prompt gamma-ray spectrometry. The number of ^{10}B atoms conjugated directly to the PEG-BSA was estimated to be 24. ^{10}B concentrations in tumor cells (2×10^5 /well) obtained 0, 3, 6, 9, 24 hrs after incubation with ^{10}B-PEG-BSA were 0, 1.75±0.45, 3.56±0.60, 4.97±0.49, and 13.01±1.74 ppm respectively. AsPC-1 cells were suspended in 125 ppm ^{10}B-PEG-BSA and irradiated with 1×10^{12}, 2×10^{12}n

/ cm ^{2} of thermal neutrons and incubated for 8 hr. in preliminary conditions. Cell growth was assayed by the incorporation of ^{3}H-TdR in the incubation. Cancer cell cytotoxicity was showed by NCT reaction with existence of boron atoms in ^{10}B-PEG- BSA.

It is said that the ^{10}B concentration between 15 and 30 ppm are necessary for effective boron neutron capture therapy. These data indicated that the ^{10}B-PEG-BSA were getting close to the lowest acceptable limit of 15 ppm, and increasing the ^{10}B binding site of the BSA, we could increase the ^{10}B uptake levels in the tumors for BNCT.

Development of a real-time prompt gamma-ray imaging system using GAGG:Ce or SrI_2:Eu scintillator array for BNCT

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During the BNCT irradiation, prompt gamma-rays with the energy of 478 keV are emitted by the reaction between thermal neutron and ^{10}B. Boron concentration can be estimated using the measured counts of prompt gamma-rays and thermal neutron flux. We already developed real-time thermal neutron flux monitor for BNCT. In this research, we also developed a real-time prompt gamma-ray imaging system using Ce doped $Gd_3Al_2Ga_3O_{12}$ (GAGG:Ce) or Eu doped SrI_2 (SrI_2:Eu) scintillator array combination with multi-anode photomultiplier. We report the overview of developed imaging system and the results of performance test.

GAGG:Ce scintillator has characteristics such as higher light output, shorter decay time, better energy resolution compared with BGO scintillator that is usually used for the gamma-ray imaging. GAGG:Ce contains Gd with the high capture cross section for thermal neutron. If GAGG:Ce is used in BNCT irradiation field, the sufficient shielding is needed. On the other hand, SrI_2:Eu has the characteristics such as higher light output, better energy resolution, compared with GAGG:Ce scintillator. It is necessary to set sufficient gamma-ray shield because the decay time of SrI_2:Eu is longer than that of GAGG:Ce. Scintillators are coupled with multi-anode photomultiplier of H8500C. Each readout signal of photomultiplier is shaped and amplified by multi-channel amplifier and converted to digital signal to obtain energy spectrum of prompt gamma-rays. A gamma-ray collimator is set in front of scintillator array. This system is surrounded by lead and ^{6}LiF ceramic plate to shield back ground gamma-rays and thermal neutrons, respectively. Performance test using ^{137}Cs gamma-ray source was performed.

It was confirmed that gamma-rays of 662 keV was measured at each readout channel with the energy resolution of less than 9% and 6% for GAGG:Ce and SrI_2:Eu, respectively. The gamma-ray image from ^{137}Cs source was measured by using the region of interest around 662 keV of energy spectrum for each scintillator.

It was shown that this system was able to detect the image of prompt gamma-ray emitted from the reaction between thermal neutron and ^{10}B. We have a plan to use MPPC array for GAGG:Ce scintillator in order to improve the energy resolution. In the near future, this system will be applied to BNCT irradiation field to detect boron distribution. Furthermore, it will be confirmed which scintillator is suitable for BNCT irradiation field.

Novel ROS-scavenging, Boron-Cluster-containing Nanoparticles for Highly Effective BNCT with Low Adverse Effects

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A boron delivery system that leads to high therapeutic efficiency and low adverse effects is crucial for the success of boron neutron capture therapy (BNCT). Herein, we developed boron-cluster-containing redox nanoparticles (BNPs) via polyion complex formation, using a newly synthesized poly(ethylene glycol)-polyanion (PEG-polyanion; possessing a ^{10}B-enriched boron cluster as a side chain of one of its segments) and PEG-polycation (possessing a reactive oxygen species (ROS) scavenger as a side chain of one of its segments). The BNPs demonstrated high colloidal stability under physiological environment, higher cellular uptake into tumor cells than that in normal cells, and low toxicity towards tumor cells without thermal neutron irradiation. Prolonged blood circulation, and specific accumulation and long retention of BNPs in tumor tissues were confirmed after its systemic administration to tumor-bearing mice. After thermal neutron irradiation, significant suppression of tumor growth was observed in the BNP-treated group, with only 5 ppm ^{10}B in tumor tissues, whereas at least 20 ppm ^{10}B is generally required for low molecular weight (LMW) ^{10}B agents to obtain satisfactory therapeutic effects. In addition, increased leukocyte levels were observed in the LMW ^{10}B agent-treated group, whereas BNPs did not increase the leukocyte level even after thermal neutron irradiation, probably due to its ROS scavenging ability. No visual metastasis of tumor cells to other organs was observed 1 month after the irradiation in the BNP-treated group, which is in sharp contrast to the LMW ^{10}B agent treatment. Our BNPs also showed that ROS scavenging did not reduce the therapeutic effect of BNCT, indicating that tumor cells were killed by α particle and Li nuclei released by the neutron capture nuclear reaction but not by ROS. The above results strongly suggest that BNPs are expected to be a promising candidate for high performance BNCT.

Development of a 3D cell culture model for depth dependent BNCT efficacy evaluations of boron containing magnetic nanoparticles

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The key for a highly efficient tumor therapy with minimal adverse side effects for the patient lies in the successful and specific delivery of the therapeutic agent to the tumor site. This is especially of upmost importance for boron neutron capture therapy (BNCT), since the rate for a successful therapy is directly correlated with the accumulation of the boron compound in the tumor region, e.g. glioblastoma. However, the achievement of a sufficient drug concentration is one of the major problems in BNCT, which is why in the last years many new formulations and approaches have been developed. Among others, the combination of BNCT with Magnetic Drug Targeting (MDT), which refers to the linkage of boron compounds on superparamagnetic iron oxide nanoparticles (SPIONs) and, after intra-arterial application, accumulation in the region of interest by an external magnet, seems to be very promising.
In order to examine the BNCT related efficacy of such synthesized BSH-loaded magnetic nanoparticles, we developed a 3D phantom model, capable of mimicking physiological tissue, especially the chemical composition concerning nitrogen and hydrogen content. This model consists of multiple 1 mm thin agarose layers, which can be stacked to a construct of several centimeters in total thickness. This setup allows the possibility to replace one agarose layer at the desired depth with a punched layer, in which cell spheroids can be placed. Cell spheroids are artificial 3D constructs of cells that resemble more closely in vivo conditions compared to conventional 2D cell culture. In this case the spheroids consist of a co-culture of F98 glioma rat cells and normal human dermal fibroblast cells and prior to the mounting into the phantoms they are treated with the boron-containing nanoparticles. Afterwards the phantoms are irradiated at the neutron source of the prompt gamma activation analysis (PGAA) facility of the Forschungs-Neutronenquelle Heinz Maier-Leibnitz (FRM II) research reactor in Munich, Germany. The thermal neutron flux equivalent chosen for the measurements was approx. 2×10^9 neutrons/cm²s in air. 24 h after irradiation, the toxicological effects on the cells are in detail analyzed in a flow cytometer. In conclusion, our 3D phantom model enables the depth dependent examination of the BNCT efficacy of boron-containing nanoparticles, and can lead to a reduction of lavish and expansive animal tests.
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PGNAA facility for BNCT at RA-3: numerical approach towards beam requirements

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The possibility of measuring ^{10}B concentrations in biological samples for Boron Neutron Capture Therapy (BNCT) is a very important capability. There exist different methods, with different features and constraints, to obtain this information. However, the one that allows for almost real-time measurements is the Prompt Gamma Neutron Activation Analysis (PGNAA). A facility for such a technique is being developed and constructed in the Channel 4 of RA-3 reactor by the Argentine National Atomic Energy Commission (CNEA). The aim of this development is being able to measure micrograms of ^{10}B in a few minutes of irradiation, conditions that are very important for research, development, and specifically for clinical related assessments. To fulfill these requirements, it is necessary to provide a high thermal neutron flux (ϕ_{th}), and to reduce as much as possible epithermal (ϕ_{epi}) and fast (ϕ_{fast}) neutron, and gamma fluxes as the beam passes the sample irradiation position and its surroundings. Numerical simulations have been performed with MCNP particle transport code to assist the design process. Different designs of collimators/filters assemblies were proposed and simulated searching to adjust the shape of the neutron beam coming from the core, according to the requirement of a high ϕ_{th} at the irradiation position for the development of BNCT activities. All of them consider narrow beams that would be manageable in preliminary characterization measurements. Initially, simplified preliminary models and sources were used for initial estimations, characterizations and adjustments of variance reduction techniques (VRTs). After that, more complex and realistic models have been developed in order to obtain more accurate estimations and better characteristics of the beam at the irradiation position. Specifically developed criticality-calculation-based track-by-track (TbT) sources have been implemented for more suitable inputs to the simulations. VRTs have been progressively used in order to reduce simulation times and/or improve the statistics of the results. The impact of different components of the design was evaluated simulating the channel with or without collimators and/or filters. Important feedback to the models was provided by measurements of sequentially built arrangements. The last analyzed configurations consider 30 cm long sapphire filter and the addition of a collimator close to the irradiation position. With them, calculations of thermal neutron fluxes above ~$1.5 \cdot 10^7$ n/cm^2·s were obtained, with ϕ_{epi}/ϕ_{th} and ϕ_{fast}/ϕ_{th} ratios below 0.03% and 0.06%, respectively. The obtained beam radii around the sample position are about 1.4 cm and 1.7 cm for ϕ_{th} above 50% and 10% of the average in the irradiation position (1.25 cm radius sphere), respectively. These most recent designs provide fluxes near minimal requirements which means that, with some simple improvements --e.g. widening the beam, better conditions can be achieved. The outcome of the different simulations and measurements provide important information for feeding the design and development of the facility. Considering them, future numerical and experimental work on designs would allow to achieve the required flux conditions and to move towards a final design stage.

The Neutron Therapeutics Solid Lithium Neutron Target for Accelerator-Based BNCT

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A new solid lithium target for accelerator-based BNCT has been developed by Neutron Therapeutics. The target is capable of converting un-scanned proton beams exceeding 100 kW from Neutron Therapeutics' electrostatic accelerator into neutrons for BNCT. The target consists of a rotating disk made up of replaceable segments (petals) around the periphery. A sheet of solid thick lithium is bonded to the surface of each petal. The target has been designed to meet the safety, reliability, and serviceability required in a hospital setting. Quick robotic petal exchange and real time monitoring of beam position and intensity are important features of the design. The present status of the target as well as test data on target lifetime and neutron yield will be presented.

A Multi-beam DD Neutron Generator with an Internal Cylindrical Moderator: Its First Operation and Possible Use for Neutron Capture Therapy

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A hybrid neutron generator using four beams of deuterium ions to strike a cylindrical titanium target with an integrated internal moderator has been fabricated and its neutron yield and flux measured. The titanium target is in direct contact with the moderator, which is designed quickly moderate the fast neutrons to thermal energies and to concentrate this radiation at its center where samples can be irradiated. Its maximum fast neutron (2.5 MeV) yield has been measured to be 4 x 10^{10} n/sec, while its thermal (< 0.5 eV) flux is 4 x 10^{7} n/cm^{2}sec. MCNP simulations of the expected yield and thermal flux match the measured results. The total supplied power is approximately 7 KW and the diameter of the generator plus moderator is 1.5 meters, thus such a generator is easily installed in small laboratories.

The generator's design and operating characteristics are presented and its possible use as a Neutron Capture Therapy (NCT) source is discussed. The DD110MB provides us a tool to improve and benchmark our simulation design for larger systems, and proves the feasibility of running multiple neutron generators heads from one control electronics and power supply rack. For NCT research the present DD110MB could also be suitable for small animal testing. Compared to some other methods of producing neutrons, the DD110MB does not use radioactive materials but instead the deuterium-deuterium fusion reaction. Thus a minimal amount of unwanted activation and radiation is produced. This provides reduced administrative and safety requirements. The generator is designed to have a long life, and has an open vacuum (turbo pumped) system, permitting easy access for maintenance and component replacement and repair.

Previously, designs using either the DD or DT fusion reactions have been considered for NCT. Such sources are less expensive and can be more compact than accelerator or reactor sources but require higher yields from those available at the time presented. Calculations by others show that for single-beam generators, one must start with fast neutron yields of 10^{12} to 10^{13} n/sec to achieve adequate thermal fluxes at the tumor site while maintaining high therapeutic ratio. Higher yields and fluxes can be achieved using the DD110MB by adding more ion beams and increasing the acceleration voltage. Simply increasing the acceleration voltage of the DD110MB from the present 120 kV to 160 kV, and adding another ion beam, will increase the fast neutron yield to 10^{11} n/sec and the thermal flux at the sample site to 10^{8} n/cm^{2}sec. Our MCNP calculations show that we can reduce the required fast neutron yield by roughly an order of magnitude by using multiple ion beams and a cylindrical target and moderator that surrounds the patient at the cancer site location. Larger cylindrical moderators fashioned to fit the patient's head or body are considered. Both brain and liver cancer have been modeled using MCNP using a variety of moderating materials.

Gamma-ray Production from a Proton-Lithium Neutron Source and Its Impact on Boron Neutron Capture Therapy

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The boron neutron capture therapy (BNCT) has been practiced in nuclear reactor facilities. However, strict safety regulations and public acceptance of nuclear reactors limit the wide deployment of BNCT. To overcome the current obstacle of reactor-based BNCT, accelerator neutron sources have been suggested to use for BNCT. Among neutron producing reactions, the ^{7}Li(p,n)^{7}Be reaction is one of the best candidate reactions for production of neutrons in accelerator-based BNCT. This reaction has a low reaction threshold (1.880 MeV), thus allowing for using a small accelerator to produce neutrons. In addition, the neutron energy from near-threshold reaction is only up to around 100 keV. A neutron moderator to lower the neutron energy to be optimized for treatment can be compact or unnecessary.

On the other hand, when lithium is bombarded with protons, gamma-rays are also emitted from side reactions ^{7}Li(p,p' γ)^{7}Li or ^{7}Li(p, γ)^{8}Be. These gamma-rays may introduce a large radiation dose to a patient. In particular, the ^{7}Li(p, γ)^{8}Be reaction emits considerably high energy gamma-rays up to 18.9 MeV. The high energy gamma-rays may have a large impact on the patient dose. To estimate the patient dose, nuclear data of the gamma-ray reactions are necessary but existing data are not satisfactory. This situation motivated us to perform the present measurement.

We measured the angular distributions of the gamma-rays from production reactions ^{7}Li(p,p'γ)^{7}Li and ^{7}Li(p,γ)^{8}Be. We fabricated two Li targets, which have thick and thin layer of Li respectively. The Li targets were irradiated with a proton beam from a Pelletron accelerator of the Tokyo Institute of Technology. Emitted gamma-rays were detected with an anti-Compton NaI(Tl) spectrometer. In this contribution, present experimental results, comparison with previous measurements, and its impact on dose evaluation will be given.

Optimum Neutron Energy Spectrum as the basis of Tunable Moderators for Next Generation Accelerators of Boron Neutron Capture Therapy (BNCT)

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Introduction

Optimum neutron energy spectrum (ONES) is the spectrum almost uniquely determined to each tumor and represents therapeutically the most effective energy spectrum for its BNCT. For next generation BNCT, moderators accompanying accelerators can be tunable to the ONES of each patient. This arrangement is in contrast to the current practice, in which a medically suitable treatment plan is designed for each patient for the pre-set neutron beam generated by the un-tunable moderator. Currently, engineering design of tunable moderators is yet unavailable, but using simple cases, we demonstrate how ONES is determined. The therapeutically most effective BNCT thus becomes in reality when technical progress is made for the design of tunable moderators. Note that the neutron fluence and treatment time are also minimized.

Materials and Methods

ONES consists of the neutron energies that are uniquely determined for *each* voxel in the tumor by maximizing the therapeutic ratio D_T / $MaxD_N$ for the voxel dose D_T and the maximum dose of normal tissues $MaxD_N$. The intensities at those energies are then determined to optimize the dose-volume histogram (DVH). Here, the absolute values of the intensity and dose of ONES are in proportion to $MaxD_N$, taken to be the allowable dose limit of normal tissues in each clinical treatment. The computational procedure for ONES amounts to solving the inverse problem of the usual Monte Carlo simulations. Note that D_T and $MaxD_N$ depend on the Boron concentrations in the tumor voxels and normal tissues, with which the ONES simulation is carried out.

Results

For illustrative purposes, we first show a simple simulation using a cylindrical brain phantom. A tumor is represented by a string of voxels along the incident beam direction. In this case, the simulation outcome from each voxel tells us how the optimum energy and therapeutic ratio vary by the tumor depth. We find the dependence to be quite strong: As the depth increases from 0 to 10 cm, the optimum energy increases from the thermal energy to 10 keV, but not exceeding 10 keV, and the therapeutic ratio decreases nearly by a decade and becomes below a clinically desirable value of 3 at about 6.3 cm. This finding demonstrates the need of tunable moderators for BNCT. We second show an illustrative application to clinical treatments, using a simple simulation of malignant glioma with 56 voxels placed in modified Snyder brain model, similar to a clinical BNCT [S.-I. Miyatake et al., *J. Neurosurg* **103,**1000-1009 (2005)].

Conclusion

Optimum neutron energy spectrum (ONES) is demonstrated to be therapeutically effective for BNCT. ONES is expected to vary appreciably from tumor to tumor, and thus moderators for such application should be then tunable to ONES for each patient. Progress is highly needed in the technological design of tunable moderators for the next generation of accelerator-based BNCT.

Enhancing resolution in neutron autoradiography of tissue samples by UV-C sensitization

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Only a small number of techniques allow precise studies of boron microdistribution, being the neutron autoradiography an attractive option due to its high resolution and relative low-cost. In order to enlarge the nuclear tracks that give rise to the autoradiographic image, a chemical etching must be performed to the nuclear track detector (NTD) after irradiation with thermal neutrons. A bulk etching velocity (V_b) characterizes this process, and its value depends on the material and the chemical attack conditions.

The spatial resolution of boron distribution can be enhanced by using the same section for the histological analysis and neutron autoradiography, as we previously reported for the quantitative autoradiography approach (QTA) in polycarbonate (Lexan^{TM}). Moreover, if both tissue structures and nuclear tracks are simultaneously observed, a more precise knowledge of the localization of boron atoms could be achieved.

In previous studies, we used the photodegradation mechanism of polycarbonate by UV-C exposure in order to improve spatial resolution in autoradiographic images. We set up this methodology for cell cultures and applied it for the quantification of boron uptake in different melanoma cell lines. The aim of the present work is to extend the UV-C autoradiography technique for the analysis of the microdistribution of boron in tissue sections.

As photodegradation of polycarbonate by UV-C is a surface reaction, the bulk velocity of an exposed NTD increases. If the *biological sample-detector* assembly is exposed to UV-C, the region of the foil in contact with the sample undergoes the UV damage in a different way than the uncovered foil. Thus, the etching solution attacks the surface at different velocities and an imprint of the biological material is formed on the NTD, which is simultaneously revealed with nuclear tracks.

The autoradiographic images for tissue samples exhibited significantly different characteristics compared to those from cell cultures, so all the steps involved in the technique had to be revised, in order to find new optimal conditions: **(a)** Tissue thickness: the thinner the sample, the sharpness of the imprint increases. For this application, 10 µm sections were more adequate than 30 µm used in QTA. **(b)** Neutron fluence: the optimal value (10^{12} n.cm^{-2}) resulted 10 times lower than the one established for cells. **(c)** UV-C exposure time: 10 min of UV-C irradiation were enough in order to obtain clear imprints, whereas 6 h were necessary for cells. **(d)** Etching conditions: KOH solution at 70ºC, for 4 min.

In some cases, track density and contrast of the pits seemed to be diminished. Possible track fading in the UV-C exposed foils was evaluated, in order to quantify the loss of tracks due to UV-C irradiation of the NTD.

Preliminary measurements of tumoral and normal tissue samples were performed with this new approach and the results were compared with QTA. Besides, UV-C absorption might be different for each tissue sample, so transmittance is being measured by UV spectrometry.
This enhanced technique could be used for certain applications where the tissue regions to be evaluated are too small and the resolution limit of conventional autoradiography is reached.

Development of remote-changeable Bonner-sphere spectrometer for QA/QC in BNCT

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Research and development into several types of accelerator-based irradiation systems for boron neutron capture therapy (BNCT) is underway. In the near future, BNCT using these newly developed irradiation systems may be carried out at multiple facilities across the world.
Considering this situation, it is important that the estimations for dose quantity and quality are performed consistently among several irradiation fields, and that the equivalency of BNCT is guaranteed, within and across BNCT systems. Then, we are establishing the quality assurance and quality control (QA/QC) system for BNCT irradiation field. As part of the QA/QC system, we are developing estimation method for neutron energy spectrum using Bonner sphere.

For our spectrometer using Bonner sphere, liquid such as pure water and/or boric acid solution is used as the moderator. A multi-layer concentric-sphere case with several sphere shells is prepared. The moderator and its diameter are changeable without entering the irradiation room, by the remote supply and drainage of liquid moderator in the several layers. For the detector, activation foils are remotely changed, or online measurement is performed using SOF (scintillator with optical fiber) detector containing boron, etc. The development of this remote- changeable Bonner-sphere spectrometer is reported.

On the assumption of the application in a typical BNCT irradiation field, the combination of the moderators for boron-10 (B-10) concentration and diameter was optimized by our originally-developed method, “High Independence Selection (HIS)”. For the B-10 concentration, the selection was performed among ten values such as 0, 0.01, 0.016, 0.028, 0.048, 0.082, 0.14, 0.24, 0.41 and 0.7 weight percent (wt%). For the diameter, the selection was performed among ten values from 11 to 20 cm in 1 cm increment. Manganin foil was assumed to be used as the detector, which has high response mainly to thermal neutrons. The optimized combination was decided among one hundred and one combinations; the combinations of ten B-10 concentrations and ten diameters, additionally the case of manganin foil only without the moderator.

The optimized combination was selected by HIS as follows: manganin foil only, 0.7-wt% boron acid solution of 13 cm in diameter, 0.7-wt% boron acid solution of 18 cm in diameter, 0-wt% boron acid solution (namely pure water) of 18 cm in diameter, and 0.028-wt% boron acid solution of 20 cm in diameter. Then, the optimized structure of the spectrometer was decided as follows: three sphere shells such as 13, 18 and 20 cm in diameter, and three liquid moderators such as pure water, 0.028-wt% boron acid solution and 0.7-wt% boron acid solution. It is not thought that this structure is necessary to be changed when the detector is changed from manganin foil to boron-containing SOF detector.

We have a plan to make the remote-changeable Bonner-sphere spectrometer, based on the optimization result. Additionally, we have a plan to perform the spectrometry experiments at Kyoto University Reactor (KUR), etc., in order to confirm the efficacy of this spectrometer.

Computational dosimetry by Monte Carlo calculation for several BNCT facilities with new treatment planning system "Tsukuba-Plan"

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A project to realize boron neutron capture therapy (BNCT) using the linear accelerator (iBNCT project) is now in progress by University of Tsukuba with High Energy Accelerator Research Organization and some institutes. In the iBNCT, we have been developed not only accelerator but the peripheral devices such as treatment planning system and patient monitoring systems.
With regard to treatment planning system, we developed general purpose treatment planning system "Tsukuba-Plan" with parallel computing system to achieve a high-speed calculation. The Tsukuba-Plan is equipped with many functions that are useful for clinical BNCT. Above all, characteristic function that selectable various beam source to compare the dose evaluation for different institutions has been equipped. At present, we have just begun to perform verifications for Tsukuba-plan at several BNCT facilities in Japan by installing the system with the beam source information for each facility.

We have already reproduced the energy spectrum of the neutron beam generated from the developed target by iBNCT project, and we incorporated it in Tsukuba-Plan as beam source information. We confirmed the depth distribution of neutron flux for various energies and two-dimensional dose distribution in a simple water phantom by using the beam source. Also, we confirmed that a dose calculation was achievable about not only the simple water phantom but also complicated model that made from a CT images of the human phantom.
However, the calculated beam source information of the iBNCT project has not been verified with some physical measurements. In the future, there is a need for verification of the beam source information with detailed physical measurement.

Furthermore, it was equipped with the beam source information of Kyoto University Research Reactor (KUR) in Tsukuba-Plan. By representing the beam source as well as geometry at around beam aperture for KUR with Tsukuba-plan, we acquired the depth distribution of the neutron flux in the water phantom using Tsukuba-Plan. The calculated depth distribution of neutron flux for various energies were compared with measurement value, and good agreements were found. As next challenge, we are going to compare the calculated value by Tsukuba-Plan with SERA which has been used as treatment planning system for BNCT until now.

Study of polymer gel dosimeter response in neutron irradiation fields

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Introduction

The application of gel dosimeters to the characteristic evaluation in BNCT irradiation fields were reported by several researchers. These dosimeters can record three-dimensional dose information in anatomically equivalent phantoms and their composition is soft-tissue equivalent. Moreover, enhancing sensitivity to specific dose component by the addition of some compounds including nuclei with high neutron capture cross section, the separation of dose components can be achieved by comparison of the response of several kinds of dosimeters. Although these dosimeters have unique dosimetric features, their response is not independent of the type of particle and its energy. For the discrimination of the dose components, it is important to evaluate the gel dosimeter response to high LET radiation more accurately. In this work, the response of polymer gel dosimeters in BNCT irradiation fields were measured and compared with the calculated dose of charged particles.

Materials and methods

The response characteristics of MAGAT-type polymer gel dosimeters were measured. The gel dosimeters were composed of methacrylic acid (5wt%), gelatin (8wt%) and 5 mM Tetrakis(hydroxymethyl)phosphonium chloride as oxygen scavenger. A dosimeter added with 25 mM boric acid was also fabricated to enhance thermal neutron dose. To calculate neutron dose correctly, elemental composition of the materials must be determined. The elemental composition of the gelatin, only which includes nitrogen in the materials and is derived from porcine, was evaluated by using a combustion elemental analyzer. All gel dosimeters were prepared in quartz beakers with 65 mm diameter and 135 mm length to avoid extra gamma ray contamination. The dosimeters were irradiated with BNCT epithermal neutron beam of Kyoto University Reactor in air at room temperature. MRI measurements were performed using a 1.5 T scanner with a head coil. A multiple spin echo sequence was applied and transverse relaxation rates (R_2) were obtained in voxel size of $1.0 \times 1.0 \times 10.0$ mm^3 on central axis of the dosimeters. Calculations were performed using a Monte Carlo simulation code system, PHITS. Each dose component from charged particles was tallied along central axis of the dosimeters. The neutron fluxes and photon dose were also tallied and verified by using gold activation and TLD methods.

Results

The depth-R_2 profiles obtained from experiments were compared to calculated total dose and each dose component distributions. The measured distributions were different from total dose distributions and had a similar shape to the gamma ray dose distribution. The sensitivity to the proton dose was low and varied at each depth corresponding to the kinetic energy of recoil protons. For the dosimeter with boron, the increment of response intensity was small as compared to high contribution of boron dose.

Conclusion

The particle type and energy dependency of a MAGAT-type polymer gel dosimeter was confirmed. Although the energy of emitted particles from nitrogen and boron reaction is constant, the energy of recoil protons varies spatially in phantoms depending on the neutron energy spectra. For accurate dose discrimination, it is important to evaluate the sensitivity to protons in low energy range.

Compact Accelerator-Driven BNCT System Used Sealed Lithium Target

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A compact sealed lithium target is under developing for BNCT application in combination with a Dynamitron (2.8MeV, 15mA).
Low energy protons incident on lithium target are one of the most suitable reaction for accelerator-based BNCT [1, 2], because a sufficient flux and good quality of epi thermal neutron beam can be obtained by using a compact beam shaping assembly (BSA) and also radiation exposer of medical staffs can be reduced by lowering the activation of accelerator facility. However, metallic lithium has several difficulties in chemical properties (low melting point, high chemical activity and ^{7}Be production) as a target material. For resolving those isssues, we are developing a compact and sealed Li target.

A thin lithium layer (0.14mm) is set on the embossed structure of a tantalum plate and covered by a thin titanium alloy foil to confine liquid lithium and radio isotopes (Be-7, T) in the target. The low-energy and high current proton beam is passing through a titanium foil and irradiated to the lithium layer. Strong turbulent flow is arose with ribs in cooling water channels of the target and had been confirmed to be able to remove high beam flux of more than 10MW/m^2. It can reduce the irradiation area of the proton beam (42kW) down to the 60mm square on the Li target
Neutrons with the energies of less than 1MeV are produced due to the ^{7}Li(p,n)^{7}Be reaction by the irradiation of the 2.8MeV proton beams and could be moderated using a compact beam shaping assembly (1m in dia.) to meet all the conditions indicated in the IAEA-TECDOC-1223.

We are constructing a compact accelerator-driven neutron source to confirm the practical reliability of the sealed lithium target for the BNCT application in the Nagoya University.

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Characterization of the neutron beams at the IHNI-1 for BNCT

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The thermal and epithermal neutron beams at the first In-Hospital Neutron Irradiator (IHNI-1) for Boron Neutron Capture Therapy (BNCT) had been experimentally characterized free in-air at the beam ports to verify the design parameters.

An extended Bonner sphere spectrometer(BSS) was employed to measure the neutron spectra. The BSS, based on a ^{3}He proportional counter as thermal neutron sensor and nine polythene spheres with the diameters from 6.35cm to 30.48cm, was augmented by adding four boron-covered polythene spheres to make it further proper for measuring the epithermal beam. Furthermore, the bare ^{3}He proportional counter and all of the polythene spheres were covered with cadmium to distinguish thermal neutrons better. Subsequently an experimental project was designed to resolve the problems such as the restraint of the dead time of the measuring system, the deduction of the room-scattered neutron background and the count correction under the nonhomogeneous beam irradiation. The number of ^{3}He in the ^{3}He proportional counter was determined in a reference thermal neutron field. The response function of the BSS was calculated with the MCNP code and calibrated by a standard ^{252}Cf source. The neutron spectra were unfolded by adjusting the calculated neutron spectra with the MAXED code.

For each beam the thermal and epithermal neutron fluence rates were measured by gold activation technique, as well as the fast neutron fluence rate using a boron-covered ^{235}U fission chamber. The bare and cadmium-covered gold foils were irradiated in turn at the beam centre, and their activities were determined by a 4πβ-γ coincidence device. The response of the fission chamber as a function of neutron energy calculated with the MCNP code indicates that the low energy neutrons less than 10keV can be mostly shielded by the boron-covered layer. The spatial distribution of neutron fluence over the beam aperture was also obtained by means of scanning manner using a bare or cadmium-covered ^{235}U fission chamber.

The gamma air kerma rate was evaluated using the pair thermoluminescence dosimeters of TLD-700(^{7}LiF:Mg,Ti) and TLD-600(^{6}LiF:Mg,Ti). In order to achieve electronic equilibrium and simultaneously avoid the unwanted gamma rays produced by the (n,γ) reaction as possible, the TLDs were clung to the surface of a pure graphite plate to be irradiated at the BNCT beams. The TLD-700 was calibrated in a ^{60}Co reference photon field, and the difference of the deposit energy in the TLD-700 between the measured and calibrated fields was calculated with the MCNP code making use of the calculated gamma spectra.

In this work, the characterization of the neutron beams at IHNI-1 had been performed by experimental method. The results show that the experimental data are almost coincident with the calculated data in their uncertainties. At present the thermal beam has been applied for some clinical treatment cases of melanoma tumors and obtained the desired effect.

Keywords: *Boron neutron capture therapy, Neutron spectra, Bonner sphere spectrometer, Neutron fluence rate, Neutron fluence spatial distribution, Gold foil,* ^{235}U *fission chamber, Gamma air kerma rate, Thermoluminescence dosimeter.*

Development of the Neutron Therapeutics Accelerator-Based BNCT System

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Neutron Therapeutics is developing a commercial BNCT system that can be offered for sale to hospitals worldwide. This "turnkey" BNCT suite will provide all the equipment needed for a hospital to begin BNCT treatments, including accelerator, beamline, target, beam shaping assembly, patient positioning systems and control systems. The system is based on Neutron Therapeutics' 2.6 MeV / 30mA electrostatic proton accelerator and solid lithium target, which were acquired from GT Advanced Technologies in November of 2015.

The first systems will be installed as investigational devices at research hospitals familiar with BNCT, who will use them to further their clinical research programs. Neutron Therapeutics is starting the process of obtaining regulatory approvals in 2016, after which the system can be made available to a much larger group of healthcare providers. The features and expected operational parameters of the Neutron Therapeutics BNCT system will be presented, along with the latest updates on ongoing facility preparations.

Accelerator Based Neutron Capture Therapies in France

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In France, we have started in 2015, an interdisciplinary work on AB-NCT profiting of a synergy among different research institutes: Laboratoire de Physique Subatomique et de Cosmologie de Grenoble (LPSC), the Institut Laue-Langevin (ILL) and the Institut de Physique Nucléaire de Lyon (IPNL) coming from nuclear physics, with neutron and gamma detection expertise and their medical applications, the Grenoble University Hospital (CHU) and the Institut Albert Bonniot (IAB) coming from radiobiology, biological research, and clinical experience.

The main purpose of this collaboration is to enable the production of epithermal neutron fields in a hospital environment by contributing to the development of compact (accelerator based) neutron sources. In parallel, we plan to improve the understanding of the biophysical determinants of the effectiveness of treatment performing radiobiology studies by cell irradiations at the ILL and simulation modelling (see R. Delorme et al. contribution). In addition, a particular effort will be performed to understand and optimize the deleterious effects of AB-NCT on tumor cells and to characterize the potential induction of subsequent anti-tumor immune responses.

Since the beginning of the project, the major realizations have been:

- a rotating Be target design able to cope with 30 kW (20 mA of deuteron beam at 1.5 MeV) and on the thermal tests with an electron beam using the COMICAC facility at LPSC,

- the design of a Beam Shaping Assembly (BSA) adapted to this rotating target,

- the development of a neutron directional detection system to characterize and control the neutron fields before and during the NCT irradiation.

We will present the fast neutron directional detector (MIMAC-FastN) able to characterize the fluence and the angular distribution of the neutron fields produced. Using a thin foil of ^{nat}B inside the active volume, we can calibrate the detector with the same reaction that will be produced at the tumor level. We will show results of measurements of fast neutrons performed recently. We will present the design and thermal simulations of the original rotating target, with in situ regeneration capability, and the BSA adapted to it.

All these contributions will be placed in the context of a national project profiting of know-how on high current ion sources and RFQ availabilities.


International Congress on Neutron Capture Therapy
ICNCT-17
Oct. 2nd-7th, 2016
University of Missouri
Columbia, Missouri

POSTERS

Mechanism of Action Analysis for Boric Acid-Mediated Neutron Capture Therapy of Cancer

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Boron neutron capture therapy (BNCT) is a targeted radiation therapy under clinical trial in Taiwan. In 2009, Prof. Fong-In Chou of National Tsing Hua University found, in addition to borophenylalanine (BPA) and borocaptate (BSH), boric acid (BA) could also be the boron carrier for BNCT. Specifically, boric acid could be a promising agent for BNCT treatment of hepatocellular carcinoma (HCC). However, the underlying mechanism that influence tumor to normal tissue (T/N) ratio of the BA uptake and the transport process is still unclear. There are numerous reports showing that tumor microenvironment is different from the surrounding normal cells, including differential carbohydrate uptake, glucose metabolism and microenvironment pH value. Other reports also show that BA could form complexes with carboxylates, which involve covalent interactions that are reversible in aqueous solution. For these reasons, we hypothesized the differences between tumor and normal cell microenvironment may result in differential uptake of boron/BA into the liver cancer cells prior neutron irradiation. Our experimental data implied vascular permeability, glucose metabolic condition and acidic environment might regulate the transport and uptake of boron/BA into the liver cancer cells. Meanwhile, in order to accelerate the preclinical study of BA-mediated BNCT in vivo, we tried to develop a novel zebrafish BNCT assay system. For the cancer model, we established two approaches via a zebrafish xenograft model with mouse melanoma cell line B16-F10 and adapted a transgenic zebrafish line that could develop spontaneous melanoma. We demonstrated that zebrafish could absorb boron in the form of BA by retro-orbital injection. A holding device was developed to immobilize the zebrafish during neutron irradiation. This simple and economic zebrafish BNCT platform shall help us to understand the BA-mediated BNCT action mechanism and accelerate its translational pre-clinical studies in the future.

FBPA-PET predicts L-BPA concentration after amino acid preloading in HuH-7 liver tumor model

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Introduction:
In recent years extra-corporal application of BNCT was evaluated for liver primary tumors or liver metastases. A prerequisite for such a high-risk procedure is proof of preferential delivery and high uptake of a ^{10}B-pharmaceutical in liver malignancies. In this work it is evaluated in a preclinical tumor model of [^{18}F]FBPA measured by PET is able to predict the bio distribution of [^{10}B]LBPA.

Methods:
Tumor bearing mice (hepatocellular carcinoma cell line, HuH-7) were either subject of a [^{18}F]FBPA-PET scan with a subsequent measurement of extracted organs using a gamma-counter or injected with [^{10}B]LBPA with tissue samples analysed by prompt gamma activation analysis (PGAA) or quantitative neutron capture radiography (QNCR). The potential impact of L-tyrosine, L-DOPA and L-BPA preloading on the cellular uptake of [^{18}F]FBPA and [^{10}B]LBPA was evaluated and the pharmacokinetics of [^{18}F]FBPA investigated by kinetic modelling, i.e. a two-tissue four-rate constant (2T4K) compartment model.

Results:
The results show a significant correlation between [^{18}F]FBPA and [^{10}B]LBPA uptake in tumors and various organs as well as high accumulation levels in pancreas and kidneys as reported in previous studies. Preloading did not increase the uptake of [^{18}F]FBPA or L-BPA in any region and kinetic modelling showed no statistically significant difference in the biokinetics of the tumors.

Conclusion:
FBPA-PET predicts L-BPA concentration after amino acid preloading in HuH-7 liver tumor models. However preloading had no effect on the cellular uptake. Despite their difference in chemical structure and administered total dose [^{18}F]FBPA and [^{10}B]LBPA demonstrate an equivalent bio-distribution in a preclinical tumor model. Thus [^{18}F]FBPA-PET is suitable for treatment planning and dose calculations in BNCT applications for liver malignancies.

Adaption of a pin-diode detector as an online neutron monitor for the thermal column of the TRIGA research reactor

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Introduction:
Real time monitoring of the neutron field in terms of quality assurance is mandatory for a clinical or preclinical BNCT application at a TRIGA research reactor. In this work an online monitoring system was tested and adapted for the use in the thermal column, using a combination of a silicon pin-diode and a conversion foil that produces detectable tritium and alpha particles via the $^{6}Li(n,^{3}H)^{4}He$ reaction.

Methods:
The original detectors were obtained from Silicon Sensor and then modified. The detector has a surface size of 1 mm^2, was connected to a coaxial plug and fixed in an aluminum casing which was chosen cylindrical with a diameter of 2.0 cm and a height of 3.35 cm. For the converter foil lithium fluoride in natural isotope composition was evaporated on aluminum foil with 0.1 mm thickness, resulting in 42 $\mu g/cm^2$. The system is completed by a main amplifier, a multi-channel analyser, the voltage supply and a PC. The final setup was tested with reactor powers of 0.1 kW, 1 kW, 10 kW, and 100 kW, at the hot and cold end of the BNCT irradiation channel in the thermal column. Each irradiation was carried out for 30 minutes. Spectra were recorded with the pin-diode and evaluated by peak integration. Additionally gold foils were inserted into the irradiation box in order to compare the measured neutron fluxes with the count rate of the pin-diode.

Results:
Size, shape and position of peaks referring to the same irradiation did not change with time or duration, giving evidence of a good reproducibility. The count rate of the pin-diode and the neutron flux measured by gold foils showed a linear correlation for the alpha-, tritium- as well as summation peaks at all positions. Uncertainties are about 4% in flux and below 1% for the count rate. Moreover the value of counts per neutron stays constant during all irradiations.

Conclusions:
The observed linear correlation and constant counts per neutron at all positions and for all powers demonstrate a calibrated pin-diode detector to be suitable for online monitoring of the neutron flux regarding BNCT application at a TRIGA reactor.

Analysis of Biological and Physical Markers as Prospective Indicators of Tumor Response for the Individualized BNCT Treatment in a Melanoma Animal Model

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Melanoma is characterized by therapeutic resistance, aggressive clinical behavior, and predisposition to develop metastasis. Recent studies indicate that the incidence of melanoma has increased steadily in the last three decades. Application of Boron Neutron Capture Therapy (BNCT) could be an option for the treatment of melanoma. BNCT is a kind of radiation therapy that offers a suitable way to kill tumor cells without significantly harming surrounding normal tissues. Successful application of this therapy depends primarily on the ability of the boron compound to selectively accumulate in tumor cells. Over time, we performed different studies in our laboratory in order to optimize the individual application of BNCT for cutaneous melanoma treatments. Furthermore, mice implanted with one of these cell lines developed tumors with different biological and physical characteristics, showing a positive correlation between BPA uptake, percentage of viable cells and tumor temperature. The aim of these studies was to evaluate whether the observed correlation between intratumoral boron content, tumor temperature and cell viability translates into a better response to BNCT irradiation. Thus, the purpose of the present study was to optimize the application of BNCT in order to improve melanoma BNCT treatments by seeking a correlation between biological and physical markers of boron uptake and tumor response. BNCT is a kind of radiation therapy that offers a suitable way to kill tumor cells without significantly harming surrounding normal tissues. Successful application of this therapy depends primarily on the ability of the boron compound to selectively accumulate in tumor cells. Over time, we performed different studies in our laboratory in order to optimize the individual application of BNCT for cutaneous melanoma treatments. Previously, we have shown that different human melanoma cell lines have different patterns of boronophenylalanine (^{10}BPA) uptake. Furthermore, mice implanted with one of these cell lines developed tumors with different biological and physical characteristics, showing a positive correlation between BPA uptake, percentage of viable cells and tumor temperature. **Objectives:** The aim of these studies was to evaluate whether the observed correlation between intratumoral boron content, tumor temperature and cell viability translates into a better response to BNCT irradiation. Thus, the purpose of the present study was to optimize the application of BNCT by increasing dose received in tumors and evaluate therapeutic response curves vs tumor temperature in order to improve melanoma BNCT treatments by seeking a correlation between biological and physical markers of boron uptake and tumor response. **Methods:** 30 male NIH nude mice were implanted subcutaneously (s.c.) in the right flank with 3 x10^6 Mel-J cells. The animals were divided into 2 groups: 1) Sham irradiated (control group); 2) BNCT (neutron beam plus BPA, 350 mg/kg b.w.). Each mouse was labeled and irradiated in the hyperthermal neutron beam of the Argentine RA-6 research nuclear reactor

(in-air thermal neutron flux of about 4.96 10^8 n/cm^2s), shielding their bodies and exposing only the tumor. Animals were anesthetized s.c. with diazepam and ketamine (200 mg/kg b.w) and irradiated in groups of 8 for about 55 minutes. Tumor growth and histology were evaluated for 30 days post treatment. Body and tumor temperatures of each mouse were measured by infrared thermography, pre and post treatment, as a non-invasive indicator of boron uptake and, consequently, of tumor response. **Results:** Total physical dose received by the tumors was 6.88 Gy. 27.03% of the animals showed complete tumor regression (complete response) and a 36.4% tumor control was observed (partial response) after 40 days post irradiation. During the first 20 days post irradiation a significant tumor control was obtained ($p<0.001$), after which tumors began to re-grow. Infrared thermography showed that tumors with higher temperatures (and according to our previous studies, higher boron uptake relative to blood), exhibited better tumor control in terms of relative volume reduction. C**onclusion:** Temperature measurements by infrared termography appear to be a prognostic indicator of therapeutic success for optimizing the application of BNCT on an individual basis.

Using Low-dose Gamma Radiation to Improve the Therapeutic Efficiency of BPA-mediated BNCT in an Orthotropic Oral Cancer Animal Model

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Introduction: The therapeutic effect of BNCT depends mainly on the concentration of boron in the tumor, and the tumor-to-normal tissue boron ratio (T/N) or tumor-to-blood boron ratio (T/B). This investigation examines whether low-dose gamma radiation (LDR) improves the boron concentration in the tumor, the T/N or T/B boron concentration ratio, and the therapeutic efficiency using an orthotropic human oral squamous cell carcinoma-bearing animal model.

Materials and Methods: An amount of 1×10^6 SAS/*luc* cells in 20 μl was injected into the tongue of a nude mouse under anesthesia. Tumor-bearing mice were randomly divided into four groups - untreated, treated with neutron-irradiation, treated with BNCT, and treated with BNCT combined with LDR. Mice were injected with 400 mg/kg BPA by intravenous route. In the group treated with BNCT, neutron irradiation was performed at 45 min after BPA injection. In the group treated with BNCT combined with LDR, mice were firstly irradiated with 0.1 Gy gamma dose at 15 min after BPA injection, and then irradiated with neutron at 45 min after BPA injection. Micro-computer tomographic and micro-positron emission tomographic images were used to determine the location of the tumor and to calculate the radiation dosage. The volume and metastasis of tumor were determined using a bioluminescence image. The therapeutic efficiency and overall survival were measured from changes in tumor volume and a histopathological analysis of tumor regions

Results: The boron concentration in the tumor in the combination-treated group was increased by 52.2%, and the T/N and the T/B ratios were increased to 1.41-fold and 1.28-fold, respectively, compared with that in the BPA-treated alone group. After 20 days, significant body weight loss was observed in both the untreated group and in the group that was treated with neutron irradiation alone, but no such weight loss was observed in the groups that were treated with BNCT or BNCT with LDR. The BNCT and combined treatment groups had a much lower relative photon flux in the tumor regions 83 days post-treatment. Notably, tumor recurrence and cervical lymph node metastasis were observed in the BNCT group, with a 50% survival rate, whereas the tumor responded completely in the group that underwent the combined treatment, with a 100% survival rate.

Conclusion: LDR improves BPA accumulation in tumors, and increases T/N and T/B boron ratios. The combination of BPA-mediated BNCT with LDR exhibits high therapeutic efficiency, and the histopathological examination revealed none toxicity to normal tissues.

Theoretical approach based on Monte Carlo simulations to predict the cell survival following BNCT

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The therapeutic benefit of BNCT has already been demonstrated in the past with nuclear reactors for radio-resistant and non-localized tumors. A major limitation of this therapy development is the great difficulty of access to medical beams of epithermal neutrons. Another difficulty is to understand and properly plan the biological effects on the targeted and healthy tissues following a neutron irradiation. A large collaboration was initiated in France with physicists, biologists and clinicians around these two key issues of BNCT. The main objective of the project is to realize a demonstrator for neutron beam production with an accelerator dedicated to clinical BNCT. A second aspect is to use theoretical and experimental approaches to study complex biological damages caused by BNCT and characterize the potential induction of subsequent anti-tumor immune responses. The prediction of the tissue response is tricky since various components contribute to the total dose with various relative biological effectiveness (RBE). The tissues targeted by the boron compound are therefore exposed to very high-LET radiations (up to 200 keV/□m) following the $^{10}B(n,\alpha)^{7}Li$ reaction, with damages localized at the cell level, and to an additional emission of 478 keV gamma rays which contributes to the far dose deposition at the patient scale. Moreover, the interaction of slow neutrons with normal tissue has to be considered. Neutron capture on hydrogen leads to emission of a 2.2 MeV gamma and a 1.3 keV recoil deuteron while the $^{14}N(n,p)^{14}C$ reaction results in the emission of a 584 keV proton and a 42 keV recoil ^{14}C, both having also a high-LET. The final response is thus a sum of effects at various scales. We propose here to use a physical approach based on Monte Carlo simulations to identify and separate the main dose contributions at the cellular and tissue scale. The cell response to such a mixed radiation field will be, then, evaluated with the radiobiological model Nanox™. Nanox™, which was originally developed to predict RBE in the context of particle therapy, takes into account the fully stochastic nature of ionizing radiation by considering dose fluctuations both at nanometric and micrometric scales, and integrates the oxidative stress.
New dedicated cell experiments will be performed under very intense and clean slow neutron beams at the research reactor ILL (Grenoble), in order to constrain the theoretical model with cell-survival experiments, and to isolate the contribution of individual dose components experimentally, thanks to the ILL deuteration laboratory and specific set-up to separate the gamma contribution. The experiments will be performed first on human melanoma cell-lines.
We will present a general outline of our local project on the radiobiological aspect and the preliminary results on MC simulations / Nanox™ coupling for cell response prediction.

BSH delivery by angiopep-2 modified liposome and gene expression variation in glioma cells treated by a In-Hospital Neutron Irradiator

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Abstract

Glioma is the most malignant brain tumor with high degree of invasion, recurrence and mortality rate. Boron Neutron Capture Therapy (BNCT) is a binary method to selectively destroy cancer cells without damaging normal tissues based on cellular nuclear reaction, it provides a new way to treat glioma. In this study, we aim to construct a new boron delivery system using angiopep-2 (TFFYGGSRGKRNNFKTEEY) modified liposome and analyze gene expression variation after neutron irradiation. Recent studies have indicated that angiopep-2 has the double targeting abilities of BBB and glioma, which provides a new way for the targeted therapy of glioma. The targeting is mainly mediated by the low density lipoprotein receptor related protein (LRP) on the blood brain barrier. To test the targeting ability of angiopep-2 to glioma, we constructed prokaryotic expression vector of fusion protein angiopep-2-EGFP (ANG-E), ANG-E was expressed in Escherichia coli BL21 (DE3) and purified with histidine affinity chromatography column. Laser confocal microscopy observation showed that ANG-E could effectively target to glioma cells U87 MG, U251, and U87EGFR, but not to human primary astrocytes; CCK-8 analysis indicated that ANG-E modified liposome boron carrier has no cell toxicity; boron delivery efficiency was also improved with ICP-AES analysis. The maximum peak occurred at 12 h, the amount of boron in cells at different time points meet the requirement for neutron irradiation. In a brain tumor model in nude mice, boron delivery in tumor was also improved using ANG-E modified liposome as boron carriers. Besides, we also constructed ANG modified liposome with DSPE-PEG-ANG and tested its boron delivery in vitro and in vivo. To detect gene expression variation in glioma cells after neutron irradiation, irradiation experiments were performed with a In-Hospital Neutron Irradiator at the full power of 30 KW with a thermal neutron flux of 1 × 109n/(cm2 · s), then gene chip analysis and real time PCR were carried out. We screened out 37 up-regulated genes including P53, Gadd45a, P16, and Bax and 11 down- regulated genes including Bcl2. The protein expression level of Bcl2, Bax, P16, P53 and Gadd45a were also analyzed by Western blotting. In general, our study indicates that ANG could effectively target to glioma cells U251, U87MG, and U87ΔEGFR. ANG-E or ANG modified liposome could deliver BSH into glioma cells in vitro and in vivo. After neuron irradiation, expression of apoptosis and cell cycle related genes were changed in U87MG. Thus, our research not only provides a new boron delivery system, but also supplements possible evidence of the molecular mechanism for BNCT.

Key words: Glioma; Angiopep-2; BNCT; Liposome; Targeted delivery

BNCT mediated by boric acid is selectively effective in tumors in the hamster cheek pouch oral cancer model

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Introduction: It is classically described that the therapeutic advantage of BNCT for tumor versus normal tissue is based on the preferential accumulation of boron. However, we showed that selective tumor lethality can result from selective blood vessel damage rather than from selective tumor uptake of the boron compound, such is the case of GB-10 in the experimental model of oral cancer in the hamster cheek pouch. The aim of the present study was to perform biodistribution and *in vivo* BNCT studies in the experimental model of oral cancer in the hamster cheek pouch employing Boric Acid (BA) as the boron carrier. Our working hypothesis was that there would be no selective tumor uptake but that BNCT mediated by BA would exert a selective effect on tumors. Boric acid is easy to handle and prepare and is approved for use in humans, similarly to BPA, GB-10 and BSH. In addition, it is more accessible in terms of cost. In relation to dose-limiting mucositis in precancerous tissue in head and neck cancer, BA might be less radiotoxic than BPA. **Materials and Methods:** The hamsters cancerized with DMBA were used for boron biodistribution and *in vivo* BNCT studies. BA was injected intravenously at a dose of 50 mg ^{10}B/kg. Samples of blood (n=5), tumor (n=23), precancerous (n=5) and normal (n=5) pouch tissue were taken 3 h post-administration and processed for boron concentration measurements by ICP-MS. Four hamsters bearing a total of 11 tumors were irradiated at RA-3 (Centro Atómico Ezeiza) 3 h post- administration of BA (50 mg ^{10}B/kg) at a neutron fluence of 1.9 x 10^{12} n/cm^2, to deliver an absorbed dose of 5.5 ± 1.0 Gy to tumor and the dose-limiting precancerous tissue. Clinical signs, tumor response and mucositis in precancerous tissue were evaluated weekly until 28 days post-BNCT when the animals were euthanized. **Results:** Boron concentration in tumor was 33 ± 5 ppm, 35 ± 5 ppm in precancerous tissue, 33 ± 5 ppm in normal pouch tissue and 15 ± 2 ppm in blood. Tumor overall response 28 days post- BNCT was 73% (Complete Remission 64% + Partial Remission 9%), significantly different (Fisher´s exact test, p=0.0008) to the matched fluence Beam Only group (Overall tumor response 18%: Complete Remission 0% + Partial Remission 18%). Regarding radiotoxicity, only 25% of the animals (1/4) in the BA-BNCT group exhibited moderate/severe mucositis in precancerous tissue (Grade ≥ 3). **Conclusion:** A comparison of tumor control data for BA-BNCT with previous BPA-BNCT tumor response data showed no statistically significant differences. In the case of BPA-BNCT, 80% of the hamsters exhibited moderate/severe mucositis in precancerous tissue vs 25% for BA-BNCT. These preliminary and counter-intuitive data suggest that BNCT mediated by Boric Acid might be therapeutically useful for head and neck cancer, with less apparent radiotoxicity.

Development of TSPO ligand as a target compound for boron neutron capture therapy: tumor imaging potential with PET

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Recently, neuroinflamation plays a vital role in many diseases affecting in the brain, including Alzheimer's disease, multiple sclerosis and stroke. Ligands of TSPO (translocator protein), a marker for activated microglia have been used as PET tracer to reflect neuroinflamation in patients. TSPO can be found throughout the body and expressed in very low concentration in normal brain. The increase in TSPO expression is correlated to microglial activation following brain injury. Accordingly, TSPO are potential targets for evaluate neuroinflammatory changes in variety of CNS disorders and development of radioligands for PET imaging. In addition TSPO is also overexpressed in different types of cancer. Moreover, boron neutron capture therapy (BNCT) agents have been designed on the basis of TSPO overexpress in tumor cells. BNCT is highly selective type of radiation therapy that can target tumor cells without causing radiation damage to the adjacent normal cells and tissues. Enrichment of tumor cells with ^{10}B atom and subsequent irradiation with epithermal neutron to produce damaging alpha radiation in the tumor cells. Developing selective probes for TSPO specific binding is challenging due to the several drawbacks such as high plasma protein binding, low brain uptake, highly variable kinetic behavior and high lipophilicity. In the present study, to improve the structural correlation of AC5216 and PBR28 to devise a structure having a higher binding affinity and low lipophilicity. We synthesized a series of phenoxyphenyl acetamide (PBR28) and oxopurine (AC-5216) derivatives and evaluated there TSPO binding affinity against [^{3}H]PK11195. The synthesized compounds showed binding affinity (IC_{50}) values of 24.85 ± 6.55 nM, respectively. Furthermore, we designed boron-rich oxopurine derivatives binds to TSPO with high affinity, providing unique two site binding profile for boron-rich TSPO derivatives. The designed compound will be synthesized and evaluated for their potential interaction with TSPO and tumor cells. Moreover, these compounds could be used as a labeled with ^{11}C or ^{18}F to obtain PET radiotracer in order to apply diagnostic and therapeutic strategy in BNCT.

Effect of particle size of nanoparticulate L-BPA formulation on biodistribution of ^{10}B after its subcutaneous administration to tumor-bearing mice

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Introduction

The successful treatment of cancer by BNCT requires the selective delivery of large amounts of ^{10}B to tumor cells. While *p*-borono-L-phenylalanine (BPA) has been shown capable of accumulating in tumors specifically, it has some pharmaceutical drawbacks such as a rapid decrease of ^{10}B concentration in tumor.

In the present study, an attempt was made to formulate nanosuspension (NS) composed of BPA that can be expected to accumulate more efficiently than BPA-Fructose complex (BPA-Fr) after local administration. BPA-NS can give a prolonged retention of ^{10}B in tumor tissue in comparison to BPA-Fr if its local administration, i.e., subcutaneous (s.c.) administration can be applied to certain tumors.

The aim of this study is to develop the BPA-NS formulation and to investigate the effect of particle size of BPA-NS on biodistribution after its s.c. administration.

Materials and methods

BPA (^{10}B-enriched) was kindly supplied by Stella Pharma Corporation, Japan. BPA-NS using Solutol® HS 15 and soybean lecithin was prepared by a wet-milling method with a planetary ball mill. By changing the operating conditions and the processing time, two types of BPA-NS with different mass median diameters ranging from 144 nm (NS-S) and 283 nm (NS-L) were prepared.

Biodistribution of BPA-Fr and BPA-NSs was assessed using male B16F10 melanoma bearing C57BL/6J mice. BPA-Fr and BPA-NS (500 mg BPA/kg) were subcutaneously administered to the mice. Boron analysis for the samples was carried out by an ICP-AES method.

Results

After s.c. administration, mean residence time of blood (MRT_{blood}) and MRT_{tumor} of BPA-NSs were longer than those of BPA-Fr. Maximum ^{10}B concentrations in tumor (C_{max}) and time to reach C_{max} (T_{max}) were 42.9 ppm, 1h for BPA-Fr, 35.9 ppm, 6h for BPA-NS-S and 28.4 ppm, 9h for BPA-NS-L, respectively. Then, the values of area under the ^{10}B tumor concentration-time curve (AUC_{tumor}) were calculated to be 313.5 μg▪ hr/mg for BPA-Fr, 599.6 μg▪ hr/mg for BPA-NS-S and 476.9 μg▪ hr/mg for BPA-NS-L, respectively. Obviously BPA-NS-S showed significantly higher AUC_{tumor} values than BPA-Fr ($P<0.0006$). Such a difference would be due to dissimilar transport rate of the BPA formulations into the bloodstream from under skin after s.c. administration. Since BPA-Fr is a solution form, BPA molecules might diffuse rapidly into the blood. In contrast, BPA-NS needs to be dissolved prior to its diffusion into the blood and thus it

acts as a depot for supplying BPA to the blood, leading to prolonged accumulation of ^{10}B in tumor. It was also found that pharmacokinetic parameters of BPA were dependent on the particle size of BPA-NSs possibly due to the difference in dissolution rate of each BPA-NS.

Conclusion

The results demonstrated that BPA-NSs, especially with smaller particle size, were effective to prolong and control the retention time of ^{10}B in tumor tissue without significant decreased ^{10}B concentration in tumor, in comparison with BPA-Fr.

Development of Fluorescent Iron Oxide - Gadolinium Borate Multifunctional (Fe_3O_4@$GdBO_3$/SiO_2 (FITC)-FA) Nanocomposites for Combined Gadolinium and Boron Neutron Capture Therapy (GdBNCT)

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Paramagnetic Gd (III)-chelates and superparamagnetic iron oxide nanoparticles (SPIONs) are commonly used as contrast agents in MRI (Magnetic Resonance Imaging) and the emerging MPI (Magnetic Particle Imaging) techniques. One of the limitations of the current MRI technique is the problem in the visualization of cells deep within the body. Recent studies are therefore directed towards the development of SPIONs, gadolinium based nanoparticles and combined systems of low toxicity which give strong MRI signals at small doses. On the other hand, nanotechnology has made its presence also in cancer therapy. Neutron Capture Therapy (NCT) is a binary cancer treatment method. The ^{10}B (for Boron Neutron Capture Therapy, BNCT) and ^{157}Gd (for Gadolinium Neutron Capture Therapy, GdNCT) isotopes are the most studied agents in NCT that is still in its formation state. Recently, new composite materials combining ^{10}B and ^{157}Gd isotopes (GdBNCT) are being researched aiming a more efficient therapy and simultaneous MRI possibility during NCT.

Thus, this study aims at the preparation of Fe/B/Gd containing multifunctional nanocomposites using inexpensive and simple chemicals such as iron oxide, boric acid/borax, Gd (III) salts and then biofuntionalization of these nanocomposites by a fluorescent dye (FITC) and folic acid (FA). Core-shell Fe_3O_4@$GdBO_3$ nanocomposites were prepared via a hydrothermal process and analyzed by XRD, FTIR, SEM/EDX and TEM. These nanocomposites were then modified with FITC doped silica (SiO_2) shell and anchored with FA to increase the binding affinity towards folate receptors on the surface of cancer cells. The FA-anchored, fluorescent and magnetic nanocomposite particles of 40-50 nm size are not cytotoxic to human stromal cells as indicated by Flow Cytometry and Fluorescence Spectrometer measurements. NCT tests are being planned currently.

Boron Neutron Capture Therapy (BNCT) for Axillary Lymph Node Metastasis of Breast Cancer

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Introduction: Breast cancer is the most morbid malignancy in women, and in Japan about 60,000 new patients are encountered every year. Although hormone therapy, chemotherapy and molecularly targeted therapy have improved its prognosis, 30% of such patients die from distant metastases. When systematic pharmacotherapy is not effective in metastatic cases, the disease is difficult to control. In this study, BNCT was assessed for lymph node metastasis of breast cancer.
Patient: A 65-year-old woman diagnosed with right breast cancer underwent breast-conserving surgery in 1992. She also presented with left breast cancer (Luminal A) and axillary lymph node metastasis in 2001 and underwent axillary lymph node dissection, mastectomy and radiation therapy for the area left of the axillary lymph node. Although subsequent lymph node cancer and lung metastasis recurred, all tumors disappeared after both chemotherapy and hormone therapy. Nonetheless, local recurrence of the left lymph node was detected in 2010, for which chemotherapy was ineffective; therefore, intra-arterial chemo-embolization was carried out at a nearby clinic. The tumor was, however, not controlled; furthermore, palsy of the left axillary nerve was detected in 2012, and the patient complained of severe pain all over the upper left limb. Examination by 18F-fluorodeoxyglucose PET-CT (FDG-PET-CT) confirmed regrowth of the tumor (maximum SUV, 8.69); therefore, BNCT was administered in 2013.
Results: An 18F-BPA-PET study conducted before BNCT showed accumulation of BPA in the tumor, with a tumor to blood (T/B) ratio of 2.2. Since the tumor was located deep in the body, BNCT was administered to the area of the left axilla, with the patient in a sitting position, by two-gate irradiation: ventral, 5MW for 47min and dorsal, 5MW for 27min. The mean value of boron concentration in blood during BNCT was 29 ppm ventrally and 28.5 ppm dorsally. Neutron fluence on the surface of body was 3.34×10^{8} $cm^{-2}s^{-1}$ ventrally and $4.89\times10^{8}cm^{-2}s^{-1}$ dorsally. The calculated average dose to the target and the left axillary nerve was 25 Gy-Eq and 4.3 Gy-Eq, respectively. Three months after BNCT, the uptake of FDG-PET-CT by the tumor mass in the left axilla decreased dramatically (maximum SUV, 3.69). Moreover, the patient was free from the severe pain in the left arm, and the progress of paralysis ceased.
Conclusion: BNCT was effective for the treatment of metastatic breast cancer that was resistant to all other methods of treatment. This clinical case suggests the applicability of this new method to the treatment of metastatic breast cancer. Further study is warranted for its application in the clinical setting.

Boron neutron capture therapy in non-SCC patients with intractable head and neck malignancies who have no other treatment options.

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Background: Boron neutron capture therapy (BNCT) is a targeted type of radiotherapy that has a number of significant advantages over conventional external beam photon irradiation, especially in that radiation can be selectively delivered to tumor cells. We had, first in the world, treated with BNCT for a patient with recurrent head and neck cancer in 2001. In salivary gland carcinomas and sarcomas at head and neck region, unresectable cases or those with local recurrence after surgery, little efficient treatment modality has been developed. **Methods:** From December, 2001 to February, 2012, 11 intractable patients with non-squamous cell carcinoma (non-SCC) were treated with BNCT. Histopathologically, there were 7 patients with salivary gland carcinomas and 4 with sarcomas. All of them had received standard therapy and subsequently developed recurrent disease which have no other treatment options. All of the patients were received intravenously either a combination of two boron containing drugs, sodium borocaptate (BSH) 5g and borono phenylalanine (BPA) 250mg/kg or BPA 500mg/kg alone.
Then they were treated with BNCT at the Kyoto University Research Reactor Institute.
Results: All of the patients had advanced disease and 4 of 11(36%) had regional lymph nodes metastasis and distant metastasis. (1) ^{10}B concentration ratios of tumor/normal tissue (T/N ratio), as determined by ^{18}FBPA-PET imaging were mean 3.0 (2.2-4.0) for sarcomas and 2.8 (2.0-3.7) for salivary gland carcinomas. (2) Regression rates of sarcoma were CR: 2 patients (50%), PR: 2 (50%) patients and those of salivary gland tumor were CR: 4 (57%) and PR: 3 (43%). The overall response rate of both patients was 100%. (2) The mean survival time was 24.2 months and the 5year OS rates were 50% and 38%, respectively. (3) Survival times following BNCT ranged from 1 to127 months. (4) BNCT improved QOL, PS and survival times. (5) The primary adverse events were brain necrosis, osteomyelitis and transient mucositis and alopecia. **Conclusions:** Our results indicate that we could make sure that safety and effectiveness of BNCT and BNCT represents a new and promising treatment modality in patients for whom there are no other treatment options.

Design and Feasibility of a Gamma-Ray Detection System for Three Dimensional Patient Dose Imaging

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The absorbed dose in tumors and normal tissues strongly depends on the $^{10}B(n,\alpha)^{7}Li$ boron neutron capture reaction rate. Determination of this rate distribution will provide more accurate absorbed dose distribution during the administration of clinical BNCT. This dosimetric information, in turn, will lead to more refined control of BNCT treatment. To this end, we are developing a dosimetric system based on the prompt gamma-single photon emission computed tomography (PG-SPECT) technique, which allows one to map out the rate distribution of 478 keV gamma-ray productions via the $^{10}B(n,\alpha)^{7}Li$ reaction. Detection of these gamma rays requires a system consisting of at least the following three components: a high energy resolution detector, efficient shielding against gamma rays and neutrons, and a collimator of moderate spatial resolution. The detector in our design is a $LaBr_3(Ce)$ scintillator coupled to a photomultiplier tube. The gamma-ray and neutron shielding materials are lead and polyethylene with lithium fluoride, respectively. The collimation component is a parallel-hole collimator made of lead designed to have 1 cm spatial resolution. To test the feasibility of our proposed design, we simulated the response of the system with PHITS2.82 Monte Carlo simulation code and an in-house pulse simulator, and estimated the system performance to detect prompt gammas originating from boron neutron capture reactions in a water phantom. The results are presented in this poster.

An innovative neutron spectrodosimeter based on thermal and fast neutron bubble detectors

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Neutron dosimetry has essential implications in some oncological therapies such as Neutron Capture Therapy. Absorbed dose is strongly dependent on neutron energy: it is so necessary to know the whole energy spectrum in order to evaluate the biological effects.
Existing neutron spectrometers have several disadvantages, such as large sizes and limited energy range.
The aim of this study is to design a new "spectrodosimeter" for medical applications, which must be compact and must be able to detect neutron interactions in the energy range from 10^{-9} MeV up to 10 MeV for most purposes.
Different spectrodosimeter configurations have been tested using the Monte Carlo simulation toolkit Geant4. The best one consists in a box filled with alternated slabs made of polyethylene and boron rich resin, for a total size of (24 x 30 x 12) cm^3. Moreover, at different depths in the polyethylene slabs, two holes for each depth suitable to host thermal and fast neutron bubble detectors (BDT and BD-PND respectively) have been made. Thanks to the moderating and absorbing effects of polyethylene and boron resin plates respectively, it is possible to detect neutrons with initial energy on the whole spectrum of interest using only bubble detectors.
Aiming to unfold the neutron spectrum from dose measurements, a C++ code has been developed slightly modifying an old code called BUNKI: basically a FORTRAN IV implementation of the Doroshenko's iterative formula. To verify the goodness of the results, Geant4 simulations have been performed generating several beams with different energy distribution shapes (uniform, increasing, decreasing, composed): the comparison between Geant4 simulations and the unfolded spectra yields a good agreement.
Experimental tests have been carried out to assess the spectrodosimeter reliability. The neutron spectrum coming out from a 15 MV medical e-LinAc has been evaluated starting from dose measurements using BDT and BD-PND detectors clustered as above. The spectrum obtained through the unfolding code fulfills the expectations, showing up a peak in the region from 10^{-1} MeV to 10 MeV. Moreover, using the most recent standard NCRP conversion factors, the spectrum has been converted to equivalent dose, and a value compatible with bubble detectors measurements has been recovered.
Despite the basic technology involved, all the considerations here expressed confirm our spectrodosimeter as a good (and cheap) candidate for neutron dosimetry.
More accurate tests are expected by using an optimized photoconverter for e-LinAc as a source on neutron beams for BNCT research, thanks to the "e-Libans" project.

Deuteron Induced Reactions as Epithermal Neutron Sources for Accelerator-Based Boron Neutron Capture Therapy

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Deuteron induced reactions on ^{9}Be and ^{13}C were already proposed in the past for generating thermal and epithermal neutrons for BNCT. Both reactions are exothermic (Q=4.36 and Q=5.33 for ^{9}Be and ^{13}C respectively) and hence, even for relatively low deuteron energies (~1.5 MeV), provide sufficiently intense neutron fluxes. This feature makes both options very attractive to work in conjunction with the 1.5 MV ESQ machine currently under development in our group.

Being exothermic, both reactions produce a significant amount of fast neutrons. In both cases, the neutron spectrum basically consists of a strong contribution of neutrons below 1 MeV and a "tail" that extends up to 5-6 MeV (depending on the deuteron energy). For ^{9}Be(d,n)^{10}B, our previous work showed that a significant part of that tail can be removed by using a thin target, leading to an epithermal beam with acceptable beam quality. The benefit of using a thin target relies on the preferential population of some highly excited states in the residue ^{10}B. In the case of ^{13}C(d,n)^{14}N, this feature is missing, so using a thin target does not lead to any additional benefit. However, the neutron spectrum for a thick ^{13}C target is in principle as good as (or even better) the one from the thin Be target. First, the amount of neutrons below 1 MeV is about 70 % (at 0º), which is basically the same as for the thin Be (69%). Also, the total neutron yield is about 20% higher (1.90□10^{8} n/□C for ^{13}C(d,n) against 1.65□10^{8} □/mC for the thin ^{9}Be) which would allow us to reduce the required deuteron current (or the irradiation time).

Being proposed some years ago by N. Colonna et al. (Med. Phys, 26 (1999) 793-799), neutron sources based on the ^{13}C(d,n)^{14}N reaction were later investigated by Burlon et al. (Med. Phys, 28 (2001) 796-803) with encouraging results for superficial and slightly deeper-seated tumors when a D_2O moderator is used. For deep-seated tumors, where an epithermal neutron flux is required, a D_2O moderator volume is no longer the best option. Aluminum and also some fluorinated materials, such as Teflon® and Fluental®, would lead to better therapeutic qualities when the lesion is deep-seated. In this work, a beam shaping assembly made of Teflon®+Aluminum was proposed and optimized by means of Monte-Carlo Simulations with MCNP. The optimization was aimed at finding the BSA configuration that (1) maximizes the dose delivered to tumor tissues and (2) maximizes the penetration depth.

For a 30 mA beam of deuterons of 1.45 MeV on a thin Be target, previous work showed that tumor doses up to 51 Gy-Eq were feasible in 2 sessions of 1 h each. The penetration depth, in this case was of ~4.5 cm from the skin surface. For 1.5 MeV deuterons on a thick ^{13}C target comparable doses and penetration depths are feasible in half of the time (only 1h session with the same current). Also, a 2 session scheme allows increasing tumor doses up to 60 Gy-Eq and penetration depths up to 5 cm.

Blistering Characteristics of Backing Metals for AB-BNCT Neutron-Producing Target by Low-Energy Hydrogen Ion Implantation

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Relying on the excellent performance of reactor-based BNCT, accelerator-based BNCT (AB- BNCT) is being developed to realize this emerging modality for cancer treatment in hospital. The success of AB-BNCT requires all aspects of integration and optimization to be fulfilled including the front-end accelerator facility and the back-end neutron beam shaping assembly. An appropriate neutron-producing target system is of special importance to determine the stability and reliability of neutron source provided by the accelerator. Nuclear reactions driven by proton beam such as $^{9}Be(p, n)^{9}B$ and ^{7}Li (p, n)^{7}Be are most commonly adopted to produce neutron source in AB-BNCT. However, the impact of intense proton beam on neutron-producing target would cause negative thermal issues and also degrade the material properties of the target system. In particular, hydrogen-induced blistering is the most known radiation damage that would take place after high fluence of proton beam irradiation. For this reason, the aim of this study is to investigate the blistering characteristics and hydrogen diffusion on several candidate backing metals for AB-BNCT target by low-energy hydrogen ion implantation. The results are expected to be helpful for the material selection as well as the prototype design of neutron-producing target system.

In addition to the often-used Cu, other metals of Ta, Pd, and V which possess high solubility and diffusivity of hydrogen and are believed to be good candidates for anti-blistering backing were also adopted to explore the hydrogen-induced blistering characteristics in this study. In order to facilitate the blistering inspection, the surface of the metallic specimens was mirror-polished prior to hydrogen irradiation. Both of the conventional ion implanter and the plasma immersion ion implantation (PIII) were employed to conduct the hydrogen irradiation experiments. The specimens were irradiated with 100 keV H^{+} ions and 20 kV hydrogen plasma gas at fluence levels higher than 2.5×10^{17} ions/cm^2 by ion implanter and PIII, respectively. Following hydrogen irradiation, a variety of analysis techniques including OM, SEM, TEM, and SIMS were used to characterize the blistering behavior of the specimens. It was found that the blisters and craters can be optically detected on the surface of Cu specimen even under a low fluence of 2.5×10^{17} ions/cm^2. In comparison with Cu, Ta exhibits great resistance against blistering. As revealed by the SIMS-measured hydrogen depth profiles, the irradiation-induced vacancies trap a considerable number of hydrogen ions and result in a hydrogen-trapping concentration peak in Cu specimens, which could be the reason for blister formation. On the contrary, the hydrogen ions in Ta, Pd, and V prefer to diffuse or react with the metallic atoms, leading to a more even hydrogen distribution over the depth of the specimen. Therefore, a careful consideration of incorporating suitable backing material into neutron-producing target is essential to prevent the blistering issue.

Cancericidal Nuclide Neutron Knife

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Abstract：As a prototype design of IHNI, IHNI-1 completed its construction in 2010 and has come into use in clinical trials since then. For the purpose of adopting to NCT irradiation technique development and meeting requirement of certain types of cancer NCT routine treatment, we have conceived an innovative layout design of IHNI-1 called cancericidal nuclide neutron knife(CNNK) after long time of operation follow-up and studies: on one side along the core horizontal direction, a set of thermal columns will be arrayed for extracorporal irradiation of the human organs, on the other side, a mixed neutron beam will be set up for tumor NCT irradiation in a depth of 2-3cm and at the lower end of the core along the vertical direction, a vertical epithermal neutron beam will be added for deeply located tumor NCT irradiation. This layout of One Reactor and Three Beams will enable our CNNK to irradiate three different types of cancer simultaneously in one time of reactor operation, moreover, two reactivity compensate rods will be added in the core for maintaining a fuel cycle, an upper beryllium reflector equal to two compensate rods equivalent will be added to let the two compensate rods return to their original position in the core when they have been all raised to the top of the core, that is to say, one more fuel cycle can be extended, and one fuel loading is able to support two fuel cycles (nearly to the life span of the reactor). Time for refueling outage can be significantly saved for use of irradiation operation. After being verified and optimized by introducing MCNP Monte Carlo and other relevant procedures, we have obtained the comprehensive calculation outcomes and parameters of irradiation seats are given as below：

Calculation Outcomes

Nuclear reactor power: 36kw

^{235}U loading in core: 1.23kg

^{235}U enrichment: 11.53%

Reactor excess reactivity (cold and clean): 4.64 ± 0.09mk

Central control rod reactivity equivalent: 6.40 ± 0.09mk

Two safety rods each with reactivity equivalent: 6.64 ± 0.09mk

Two compensate rods each with reactivity equivalent: 6.64 ± 0.09mk

The added upper beryllium reflector reactivity equivalent is equal to two compensate rods

Parameters of Irradiation Seats

- Horizontal thermal columns: Φ_{th} (<0.4eV): 9.14E + 09 n/cm^2.s^1
- Horizontal mixed beam: Φ_{th} (<0.4eV): 0.827E + 09 n/cm^2.s^1
  (outlet, free space) Φ_{epi} (>0.4eV-10keV): 0.401E + 09 n/cm^2.s^1
  J_n/Φ_n: 0.81
- Vertical epithermal beam: Φ_{epi} (>0.4eV-10keV): 1.0E + 09 n/cm^2.s^1
  (outlet, free space) J_n/Φ_n: 0.798
- At all the irradiation seats, fast neutrons and γ-ray contamination dosage are in a reasonable range.

The calculation indicates that the innovative layout design of IHNI-1 is feasible.

Comparison of Dose Calculation Using Treatment Planning Systems THORplan and SERA for BNCT

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Introduction

National Tsing Hua University and Taipei Veterans General Hospital started a clinical trial of boron neutron capture therapy (BNCT) for recurrent head-and-neck cancer at Tsing Hua open-pool reactor on August 11, 2010. Up to January 2016, 22 patients were treated. For each treatment, one week before the irradiation, patient's averaged tumor-to-normal tissue ratio (T/N ratio) of boron concentration was obtained from PET image after injection of ^{18}F-BPA. However, it has been observed that the boron distribution in tumor region was not uniform, and sometimes far from uniform. Hence a new feature of handling distributed boron PET information for more accurate treatment planning dose calculation was developed and added to the treatment planning system THORplan.

Materials and Methods

This new capability was applied to two cases selected from previous treatments, one for code verification purpose, and the other for investigating the degree of discrepancy due to non- uniform boron distribution. The 1st case chosen is one with small GTV volume and relatively uniform boron distribution. The 2nd case chosen is one with apparently non-uniformly distributed boron easily seen from the PET image. The contour of GTV was based on MRI image as usual.

Results

In the 1st case, the averaged T/N ratio was 2.71, while the distributed boron T/N ratio ranged from 1.87 to 3.49. The dose result of using distributed boron in treatment planning was quite close to the result of using uniform (average) boron distribution. In the 2nd case, the average T/N ratio was 4.56 while the distributed boron T/N ratio varied from 0.4 to 7.64. Under the same irradiation condition, the mean dose and the minimum GTV dose were very much overestimated when uniform average boron concentration was used for the whole GTV. Even if the GTV were divided into two regions, each with its own average T/N ratio 4.58 and 1.74, the mean dose and the minimum GTV dose were still overestimated by a factor of 1.07 and 2.3 respectively compared with the distributed boron results.

Conclusion

This new capability of incorporating PET information of distributed boron provides a more accurate way of dose evaluation during treatment planning, which will be helpful for establishing the correlation between clinical outcome and the dose delivered to the patient.

ABENS-BNCT System: Verification of durability of thin layer solid lithium target for high current proton beam

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Introduction

A neutron source for a BNCT system using lithium as its target generates low energy neutrons, and cannot produce fast neutron components exceeding 0.8MeV. This means that the neutron source would be optimal for BNCT. Thus, a compact beam shaping assembly can be constructed. While, the melting point of lithium is 180.5 ℃. Until now this low melting point has caused issues concerning durability of the target in the case of irradiation by the proton beam current of the maximum specification: CW20mA. For this issue, we have performed durability tests of the target. Target substrates without evaporation of lithium on it were irradiated by electron beams. Furthermore we have verified the durability through irradiation experiments to the lithium target by using proton beams with low current which is the same current density as the electron beams. However, experiments on the target irradiated with large current beams have not been performed as far, because large current accelerators were not available. The advent of a large current accelerator made us verify the durability of the lithium target based on large current proton beams.

Materials & Methods

A cone shaped lithium target substrate was evaporated with lithium so as to form a lithium thin layer on it with a thicknesses of 50~100μm in the perpendicular direction with respect to the surface. And it was cooled with a water flow of 250L/min at 18 ℃. The proton beam was adjusted to irradiate the circular area with a diameter of 2~3cm on the central region of the target. After this adjustment, the proton beam was rotated concentrically in order to dissipate the heat generated in the target. Collimators divided into four pieces were placed at the front end of the target and the beam was irradiated concentrically with respect to the center of the target by monitoring the beam current. Monitoring the degree of vacuum in the target chamber, we aimed to increase the beam current gradually to reach the maximum value of CW20mA.

Results

The lithium layer showed a thinner thickness at the center and the circumference of the target than other regions where the layer thickness of 50~100μm could be obtained, however these regions were not required to irradiate so that it did not matter particularly. The thickness of the layer is also not necessarily required to be constant rigorously, however, currently we have facilitated a process capable of uniform evaporation. In the beam profiling, the center of the beam at the irradiation region of the target was recognizable when evaluated the center of the beam and the size under a condition of the beam current below 1mA by using gasochromic films. However the beam intensity distribution could not recognized due to the intensive beam. The shape and intensity distribution of the beam could be recognized using a thermos-camera under the same irradiation condition. In addition, with the dispersed irradiation of the beam, the

irradiation to the central region of the target could be avoided. Moreover, it was confirmed that the beam was circumferentially dispersed in the irradiation region. Prior to the irradiation with an intensive beam current, the beam profiling was mandatory. The beam diameter and the condition of dispersed irradiation were decided by using the thermos-camera. Then the intensity of the beam was slowly increased under the condition, and the irradiation with the beam current of CW12mA was performed for 5h (integral). The lithium layer showed some spots caused by the irradiation, however there was nothing wrong with the state of the lithium. In addition, the chemical activation of the lithium metal was kept as it is. Aiming at the CW20mA, we would keep adjusting the beam further.

Fricke gel detectors in high-LET and long-time irradiations for BNCT dosimetry

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Gel dosimeters shaped as layers or thin cylinders have shown noticeable potential for dosimetry in epithermal or thermal neutron fields with very high fluence rate, as those exploited for boron neutron capture therapy (BNCT). In their standard composition, these dosimeters are tissue-equivalent (TE) both for neutrons and for the secondary radiation produced by nuclear reactions. Through an analytical comparison of the results obtained with pairs of dosimeters with different isotopic composition, images or profiles of the various dose components in a TE phantom can be obtained. Thanks to the proposed geometry, neutron transport is mainly determined by the phantom material housing the dosimeters and then the change in the isotopic composition of the dosimeter does not give measurable variations of the radiation field. Two issues limit the precision achievable in BNCT dosimetry with gel dosimeters: the LET dependence of the dosimeter sensitivity and the low dose rate that occurs in these radiation fields. In this work, accurate measurements have been carried out, aimed at attaining a higher precision in the determination of the under-response factor of gel dosimeters for the dose due to the charged particles alpha and ^{7}Li generated through the reactions of thermal neutrons with ^{10}B. In order to increase the precision, great attention to all the irradiation configurations and all dosimeter calibrations has been paid. Moreover, some experiments have been carried out in order to investigate the variation in time of the dosimeter response and the influence of long irradiation times (up to 4 hours) with an absorbed dose lower than 6 Gy. i.e., the usual for BNCT dosimetry. The results also allowed to determine a more precise value of the LET quenching coefficient.The neutron irradiations were carried out at the BNCT epithermal neutron column of the LVR-15 research reactor, in Řež (Czech Republic). The dosimeters were of the Fricke–xylenol–orange type prepared by utilizing Agarose as gelling agent. The samples were shaped as layers 5 mm in thickness. Lithium fluoride thermoluminescence detectors (TLDs) have been utilized to attain the thermal neutron fluence profiles in the same positions of the gel dosimeters inside the phantom. Owing to their small dimensions and their good tissue equivalence, TLDs do not perturb the radiation field. Activation measurements with bare and cadmium-covered indium foils have been performed in order to measure the thermal neutron fluence for TLD calibration. Gamma calibrations were performed against a 6 MV photon beam from Varian Clinac DBX.

The quenching coefficient determined in this experiment (0.51) is not much different from that found in a previous experiment, in which the gelling agent was gelatin (0.55).

The results of this experiment show that, despite the various problems that affect gel dosimeters, reliable results can be obtained with these detectors for BNCT dosimetry.

Response of Fricke gel detectors to extended and high-LET irradiations in BNCT beams

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Gel dosimeters shaped as layers or thin cylinders are appealing for the dosimetry of high-flux epithermal or thermal neutron fields, such as those used for boron neutron capture therapy (BNCT). In their standard composition, these dosimeters are tissue-equivalent (TE) both for neutrons and for the secondary radiation produced by nuclear reactions. Through an analytical comparison of the results obtained with pairs of dosimeters with different isotopic composition, images or profiles of the various dose components in a TE phantom can be obtained. In our detector geometry, neutron transport is mainly determined by the phantom material housing the dosimeters, thus changing the isotopic composition of the dosimeter does not alter significantly the radiation field. Two issues limit the dosimetric accuracy of the gels in BNCT: the LET dependence of the dosimeter response and the low dose rate of these radiation fields. In this work, accurate measurements were carried out, aimed at attaining a higher precision in the determination of the under- response factor of gel dosimeters to the alpha and ^{7}Li particles generated through thermal neutrons reactions with ^{10}B. Moreover, experiments were carried out in order to investigate the variation of the dosimeter response over time and the influence of extended irradiation times (up to 4 hours) up to an absorbed dose below 6 Gy. i.e., which is usual for BNCT dosimetry. The results also allowed us to determine the LET quenching coefficient. The neutron irradiations were carried out at the BNCT epithermal neutron column of the LVR-15 research reactor, in Řež (Czech Republic). The dosimeters were of the Fricke–xylenol–orange type prepared with agarose as gelling agent. The samples were shaped as layers 5 mm in thickness. Lithium fluoride thermoluminescence detectors (TLDs) were utilized to determine the thermal neutron fluence profiles at the same positions of the gel dosimeters inside the phantom. Thanks to their small dimensions and their good tissue equivalence, TLDs do not perturb the radiation field. Activation measurements with bare and cadmium-covered indium foils were performed in order to measure the thermal neutron fluence for TLD calibration. Gamma calibrations were performed with a 6 MV photon beam from a Varian Clinac DBX. The quenching coefficient determined in this experiment (0.51) is not much different from that found in a previous experiment, in which the gelling agent was gelatin (0.55).The results of this experiment show that, overall, gel dosimeters offer reliable and accurate results in BNCT applications.

"Neobor" – European/international scientific network for BNCT research and medical training at MARIA reactor (Poland)

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BNCT facility at MARIA reactor based on uranium fission converter is under construction. Selected subsystems of the research-training neutron station have already been constructed. It is expected to run neutron beam with intensity of 10^9 n/cm^2/s for the first time in the middle of 2017 just after arrival of ordered uranium plates for converter from Russia (TVEL Company). Basing on MARIA facility the scientific network ("Neobor") is forming. Several Polish and several European research institutions have already signed the Letter of Intent for collaboration in BNCT research. Work Packages were defined for years 2016/2017. Four most important of them concern irradiation technology (tech), dosimetry (dosi), chemistry (chem) and biology (biol).

(Tech) Intelligent converter for beam intensity modulation, adjustable filter-moderator system for energy spectrum change, Pg-SPECT, collimation, beam shutter, beam stopper, beam dosimetry, room shielding and radiation protection system.

(Dosi) Station will be equipped with unique recombination detectors and methods developed in Poland for determining four components of the therapeutic dose. The set of four recombination detectors: (1) hydrogen free to measure external gamma radiation and from the capture reaction ^{1}H(n,γ)^{2}D, (2) tissue-equivalent to distinguish gamma and total neutron dose, (3) nitrogen for detect protons from ^{14}N(n,p) reaction and extracting thermal neutrons and finally (4) boron fluoride for boron dose determination from the ^{10}B(n,α)^{7}Li reaction fulfil needs of four dose determination for medical protocols in BNCT.

(Chem) Though two boron carriers, BSH and BPA, are successfully used in BNCT since many years, broader use of BNCT as clinically useful modality requires the development of new boron target compounds and complementary delivery methods. Through the now 50-year course of BNCT an array of potential boron carriers have been synthesized but none was investigated using actual BNCT experiments. Borated nucleosides are one of the best characterized and promising boron carriers for BNCT waiting in the pipeline for further development. The great advantage of this class of boron carriers, in addition to other useful in BNCT properties, is that nucleoside derivatives have been in clinical use for several decades and have become cornerstones of treatment for patients with cancer or viral infections. The knowledge accumulated on their medicinal chemistry, pharmacology and biology can be used to facilitate and accelerate the development of this class of boron carriers for BNCT. Development of innovative nucleoside boron carriers for BNCT is one of "Neobor" network targets.

(Biol) Research on boron carriers will include the synthesis and investigation of the properties of boron cluster conjugates with macromolecular carriers and small molecules. One aim is to impair

the biological activity of the T regulatory lymphocytes by boron cluster antibody conjugates, thereby enhancing the cytotoxic T cells. In addition, it is planned to use phagocytic cells as carriers of insoluble boron derivatives (boron carbide, boron nitride) to their deliver and deposit in tumour tissues. “Neobor” intended also to investigate BNCT for the treatment of certain autoimmune disorders.

Main “Neobor” scientific network partners:

- National Centre for Nuclear Research,
- Institute of Medical Biology Polish Academy of Sciences,
- Ludwik Hirszfeld Institute of Immunology and Experimental Therapy Polish Academy of Sciences
- Jan Długosz University
- Università di Pavia
- University of Tsukuba
- National Research Centre - Kurchatov Institute
- VTT Technical Research Centre of Finland Ltd

Clinical commissioning of a cyclotron-based epithermal neutron source at Southern Tohoku BNCT Research Center

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Purpose/Objective(s): A cyclotron-based epithermal neutron source (C-BENS) was installed at Southern Tohoku BNCT Research Center (STBRC) in April 2014. The C-BENS consists of mainly five parts; a cyclotron accelerator, a beam transport system, a beam shaping assembly (BSA), a collimator assembly, and a patient transport system. A cyclotron accelerator was developed by Kyoto University Research Reactor Institute and Sumitomo Heavy Industries, Ltd. and can produce more than 1 mA proton beam with an energy of 30 MeV. In a beam transport system, the proton beam is transported to the neutron production target made by beryllium plate. Emitted neutrons are moderated by lead, iron, aluminum, and calcium fluoride. The BSA was optimized to obtain a sufficient intensity of epithermal neutrons while reducing fast neutrons and gamma-ray contamination. Concerning a collimator assembly, the aperture diameter of neutron collimator is four types from 100 mm to 250 mm. we evaluated the quality of a beam to check whether a neutron beam to worth using treatment was secured. In this report, an overview of the clinical commissioning of the C-BENS at STBRC will be presented.

Methods and materials: Irradiation tests were performed by using a water phantom. It was difficult to measure a thermal neutron directly, so the foil activation method was used, which is the radio activation method generally used for the measurement of a thermal neutron. In this method, the radioactivity of radiated materials was measured based on the fact that the radioactivity caused by the neutron irradiation depends on a neutron flux and a reaction cross section. On the center of beam axis and off-axis of 5 cm, the depth dose of the thermal neutron flux was measured. The gamma-ray dose was also evaluated by using the thermo luminescent dosimeter (TLD) set in the water phantom along the center of beam axis. In addition, the Monte Carlo simulation (MCNPX) was performed in the same as condition of measurement and compared the calculation results with the measurement results.

Results: The thermal neutron flux in the water phantom at the center of beam axis was confirmed about 1.2×10^9 neutrons/cm^2/sec at 20 mm from the surface with 1 mA proton beam. The simulation results were all in good agreement with the measurement results.

Conclusions: Through clinical commissioning, the stability of a neutron beam in the C-BENS at STBRC was confirmed. In the future, it needs to be examined how the beam quality assurance should be carried out.

Preliminary study for the beam component separation using polymer gel detector containing lithium compounds

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Introduction

Polymer gel detectors have been investigated for the three-dimensional (3D) dose measurement of the complex conformal dose distributions in the clinical applications. These devices utilize radiation-induced polymerization reaction of vinyl monomer in the aqueous gel matrix to preserve information about the radiation dose. The 3D absorbed dose distribution is deduced from the created polymer distribution measured by imaging modalities such as MRI and Optical CT. Polymer gel detector is also regarded as tissue equivalent to neutron beam because the components are mainly water and a small amount of other chemicals consisting of carbon, nitrogen and oxygen. A further advantage of polymer gel detectors is that the interaction with neutron could be controlled by addition of some compounds with neutron-capture-nuclei such as ^{6}Li and ^{10}B. It means that each dose component might be distinguished from complex dose due to various primary and secondary radiations by the variety of elemental composition. In the previous work, we have investigated that the dose response of polymer gel detector irradiated by thermal neutron beam was enhanced by addition of a very small amount of ^{10}B (50 ppm). In the present work, the influence of various lithium compounds on the dose response and the stability of polymer gel detectors was investigated by high-energy photon beam before the future experiments using neutron beam.

Materials and Methods

In this work, MAGAT-type (methacrylic-acid-based) polymer gel detector was employed because of the high sensitivity. Various lithium salts (LiCl, $LiNO_3$, LiOH, Li_2SO_4 and Li_3-citrate, which have comparatively high solubility in water) containing ^{6}Li in the natural ratio were mixed into the polymer gel in the concentration of 100 and 200 ppm of ^{6}Li, respectively. The resulting gels were subdivided by pouring into test tubes. The irradiations were performed using 6 MV X-ray from a medical linear accelerator (Novaris-TX, Varian/BrainLAB) and gamma ray from ^{60}Co source. The doses upto 5 Gy were delivered to each sample. The read-out from the samples was performed using a 1.5 T MRI scanner (SIGNA HDxt 1.5T, GE Healthcare) with a head coil the day after irradiation. A multiple spin-echo sequence was applied and the transverse relaxation rate R_2 ($=1/T_2$) was obtained as the function of absorbed dose.

Results and Discussion

In the results, the dose-R_2 responses (sensitivities) of the polymer gel detectors containing $LiNO_3$, LiOH and Li_3-citrate decreased significantly (40-70% lower at 5 Gy) comparing with that of the basic gel detector without lithium salts. Also, Li_3-citrate did not dissolve enough in the gel solution and the gel was translucent. On the other hand, the gel detectors containing LiCl and Li_2SO_4 showed the comparable sensitivity to the basic gel detector and the rather sensitivity enhancement was also observed. From these results, it was suggested that LiCl or Li_2SO_4 was a suitable additive to introduce lithium to the polymer gel detector. When lithium salts containing the enriched ^{6}Li could be used, the clearer enhancement due to ^{6}Li would be expected even in a smaller amount of additive.

Dynamic Infrared Imaging in the Hamster Cheek Pouch Model of Oral Cancer: searching for prognostic parameters of tumor response and normal tissue radiotoxicity in BNCT

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Biomedical infrared thermography is a non-invasive and functional imaging method that provides information on the normal and abnormal status and response of tissues in terms of spatial and temporal variations in body infrared radiance. Employing radiometric measurements and algorithms that convert infrared radiance to temperature, this technique can be used to quantify temperature distribution on body surfaces. It is especially attractive in cancer research due to the hypervascular and hypermetabolic activity of solid tumors. Moreover, healthy tissues like skin or mucosa exposed to radiation can be examined since inflammation, changes in water content, exudation, desquamation, erosion and necrosis are factors that modify their thermal properties.

Based on our earlier experience using this technique in our melanoma patients as well as in animal research, in this work we combined Dynamic Infrared Imaging (DIRI) with theoretical and experimental studies to contribute to the understanding and evaluation of BNCT-induced tumor control and radiotoxicity in the hamster cheek pouch model of oral cancer. Particularly, we focused on the observation of temperature changes under transient conditions associated with water transfer in the tissue-air interface of tumor and normal tissue in the pouch.

We examined 70 hamsters with DIRI, divided into 6 groups: non-irradiated normal hamster cheek pouch; DMBA-cancerized pouch + BNCT mediated by boronophenylalanine (BPA-BNCT) or beam-only; normal pouch + BPA-BNCT or beam-only; and sham group (DMBA-cancerized pouch without treatment). For DIRI studies, the pouch was everted under anesthesia, during 12 minutes. Tissue thermal responses were assessed before, during and after forced temperature changes at tissue-air interface (provocation test). Since tissue temperature varied exponentially with time, we used as a first approximation, the well-known lumped capacity analysis method. Under this assumption, we modeled each transient process considering the heat transfer from tissue to ambient through convection and evaporation, to determine the typical time constant and degree of evaporation occurring on the tissue surface. We also used thermographic data to determine conduction and convection thermal parameters through an inverse problem, solving numerically the 1-dimensional transient bioheat problem formulated by Pennes equation.
Group comparisons were performed using paired or unpaired *t*-test and one-way ANOVA with a significance level lower than 0.05.

We were able to characterize thermal responses of tumors and normal tissue through a comprehensive validation of the proposed models. In particular, tissue transient processes under provocation tests could be used as a non-invasive method to characterize tissue physiology. We found significant differences in the studied parameters between tumors treated with BPA-BNCT and sham or beam-only groups. This fact might be explored further as an indicator of tumor response in a long-term study including DIRI. Finally, we observed differences in the recovery time constants after the provocation tests for normal pouches exposed to BNCT compared to non-irradiated normal pouches, which would possibly be related with their water content.

In summary, DIRI could provide ancillary non-invasive *in vivo* information related to the physiological status of tumor and normal tissue and their response to BNCT, in the hamster cheek pouch oral cancer model.

Optimum design of an electron-linear-accelerator-driven subcritical neutron multiplier for boron neutron capture therapy

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A beam shaping assembly (BSA) for boron neutron capture therapy, which uses neutrons from the Bremsstrahlung (gamma, n) reactions in a photo-neutron target irradiated by electrons from a linear accelerator (LINAC), was designed [1], and it was estimated that the epithermal neutron flux at a treatment position of 2 x 10^9 [1/cm^2/s], which has superior beam properties, is produced when a photo-neutron target that includes natural uranium is irradiated by 20 MeV electrons with a beam power of 15 kW. However, designing the photo-neutron target with careful consideration of multiplication of neutrons by fission of uranium may increase the epithermal neutron flux at a treatment position. The author therefore performed a series of simulation calculations by MCNPX for the optimum design of a subcritical neutron multiplier (SNM) that is irradiated by 20 MeV electrons from a LINAC.

The BSA model has two holes along a rectangular prism axis, one for the entrance of an electron beam from a LINAC and another for extracting the neutron beam, and is 120 x 120 x 133 cm in size. The BSA contains a rectangular SNM having a 0.5-cm-thick Zr reactor vessel where the surface area of 5 x 5 cm around the beam axis is irradiated by 20 MeV electrons, a 11-cm-thick Pb slab and a 47.5-cm-thick MgF_2 slab which have an area of 50 x 50 cm and make the proper neutron spectrum at a treatment position, a 22.05-cm-thick laminate neutron beam collimator, and so on. The thicknesses of the slabs of Pb and MgF_2 and the neutron beam collimator had been determined so that the neutron beam fulfilled specific conditions which nearly met the recommended beam-characteristics shown in IAEA-TECDOC-1223. In the SNM, the 0.392-cm-thick low-enriched U slabs in 0.04-cm-thick Zr jackets interlaminated with water zones are stacked along the beam axis, and the number of U slabs parametrically varied in five steps (2, 3, 5, 7 and 9) to alter the total thickness of U slabs as a photo-neutron target. The area of U slab as well as the thickness of water zone was determined so that each of the five SNMs met specific requirements where the effective multiplication factor (k_{eff}) of the BSA became 0.992, and the BSA had a negative moderator temperature coefficient of reactivity.

With increasing the number of U slabs from 2 to 9, the peak of the epithermal neutron flux in the SNM increased by 2.6-times due to the 1.35-times increase in the number of neutrons from the electron-induced Bremsstrahlung (gamma, n) reactions as well as the 70 % decrease in the volume of SNM, although the epithermal neutron flux at a treatment position decreased by 48 %; this is attributed to the fact that the distance between the peak positon of the epithermal neutron flux in the SNM and the treatment position increased by 10 cm due to the increase in the SNM's length along the beam axis. It was estimated that the SNM having the two U slabs produced the maximized epithermal neutron flux at a treatment position of 2 x 10^9 [1/cm^2/s] with the 11.2 kW thermal output by fission in the U slabs when the SNM was irradiated by 20 MeV electrons with a beam power of 6 kW.

[1] Faezeh Rahmani, et al., Nucl. Instr. and Meth. Phys. Res. A 641 (2011) 136-140.

Upgrade of On-line Monitoring System of BNCT Beam at THOR

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The on-line monitoring system is an indispensable system of BNCT beams for the accurate control of dose delivery. The original on-line monitoring system of the BNCT beam at THOR (Tsing Hua Open-pool Reactor) was constructed in 2005 and consisted of three pieces of miniature fission chambers mounted at discrete positions around the bismuth shield of the beam shaping assembly and just prior to the collimator. The signals of the fission chambers were processed by the standard NIM modules including preamplifiers, amplifiers, and single channel analyzers and fed to the NI (National Instrument) PCI-6602 DAQ (data acquisition) device through the NI BNC-2121 connector accessary. A LabVIEW program was written to acquire the fission chamber signals every one second and display the counting rates and delivery dose variation with time on the screen of a PC (personal computer). Because of the aging of the PC and in order to ensure the availability of the on-line monitoring system at any time, recently we constructed a new parallel data acquisition and display system to serve as a stand-by on-line monitoring system or even to replace the old system. In the upgrade system a stand-alone NI USB-6341 DAQ device was employed to replace the PCI-6602 DAQ device combined with the BNC-2121 counter accessary. The data acquisition of the fission chamber signals every one second and the display of the counting rates as well as the delivery dose variation with time were controlled by a blank new LabVIEW program. The LabVIEW program was designed in four Window pages, namely, Preparation, Main window, THOR status, and Settings. The Preparation page is used to register the responsible personnel of each specialist group for the current operation and input the target dose, background and boron dose rates, and calibration data of each fission chamber. The Main window mainly plots time variation of counting rates of each fission chamber and the delivery dose and shows their currently updated data. The THOR status page simply shows the currently operation power of THOR. The setting page is used to assign the folder path of the log data and report files and also shows the default setting of the USB-6341 DAQ with respect to the fission chambers. During the system upgrade we have also checked the dead time correction of the counting system and included the gamma-ray monitor at the treatment room to the new on-line monitoring system.

Neutron Activation Analysis Using BNCT Beam at THOR

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Neutron Activation Analysis (NAA) is a well-developed method for the determination of element composition in a test sample. NAA is particularly useful for trace element measurement, however, it can also be used for minor and major elements determination. In this work we conducted NAA by using the BNCT beam at THOR to irradiate the test sample located along the center axis at a depth of 2 cm, where the thermal neutron flux is the maximum, of a 20 x 20 x 20 cm^3 PMMA phantom directly contacting the beam exit. Simplicity and convenience are our emphases and high degree of accuracy is not our pursuit, thus we choose absolute calibration method for analysis to avoid the necessity of the preparation of calibrators containing a known amount of the element(s) of interest, which is sometimes not easy to achieve. In our BNCT beam an equivalent surface neutron source has been well-characterized with space, energy as well as angular distributions, and a process of verification and validation has been made. Therefore, the reaction rate per atom of any interest element in the sample at the irradiation position for a specific source strength can be calculated by using MCNPX Monte Carlo code. In addition, there is an on-line neutron monitoring system installed in our BNCT beam, which was well-calibrated in terms of source strength per cps (counts per second) of neutron monitors. As a result, the time-dependent reaction rate per atom produced during the irradiation time can be taken into account by applying the counting rates acquired by the neutron monitoring system. The NAA method applied in our BNCT beam, for which the reaction rate per atom of the interest element is derived from a Monte Carlo code calculation and the effect caused by time-dependent neutron flux is precisely corrected, is called by us the modified absolute calibration method. By using this modified absolute calibration method proposed in this work, first of all we conducted a test measurement for three activation foils with given compositions, namely, Au(1%)Al, Mn(88%)/Ni, and Cu(100%) used in our BNCT beam for routine QA/QC. It was found that the measured Au, Mn and Cu compositions agreed excellently with the specification values so as to demonstrate the proposed modified absolute calibration method being a good and adequate NAA method. Following the test measurement, we proceeded to measure a CaF_2:Mn TLD chip with dimensions of 3.2 x 3.2 x 0.89 mm^3 used for gamma-ray QA/QC of the BNCT beam. The weight percent of Mn was determined to be 1.6% agreed very well with the data measured by the direct comparator method. Finally, the proposed modified absolute calibration method was applied to measure some conventional food and dietary samples, such as salt and Centrum□.

The design for BNCT facility based on radiation dose estimation

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The combination of Li target and high power proton accelerator is very innovative for Boron Neutron Capture Therapy (BNCT) because of its high neutron production capacity. We are investigating the feasibility and stability of a confined Li target and a proton accelerator of 2.8MeV and 42kW (IBA Dynamitron) and constructing Nagoya University Accelerator-driven Neutron Source (NUANS) for performing experiments. Careful radiation protection for patients and the environment is necessary because fast neutrons and gamma rays are produced associated to moderating neutrons to an epithermal energy region. Considerable radiation are emitted from the neutron source when a desirable epithermal neutron beam of $>10^9$ cm^{-2} s^{-1} is produced. The shielding material has the major amount of weight around the neutron target and that cost is also considerable. Therefore compact shielding system is very beneficial for making installation cost lower and handling easier. We estimated the radiation dose with a Monte-Carlo simulation code of Particle and Heavy Ion Transport code System (PHITS) based on nuclear reaction data of ENDF/B-VII.1. The shield of whole facility consists of the Beam Shaping Assembly (BSA) shield, which covers the side and upper stream of BSA, the BSA room shield and the building shield (from inner to outer). We optimized the shield of whole facility keeping the neutron yield high with a new designed BSA. We selected borated polyethylene and concrete as the majority of shielding material because of their shielding ability and costs. This design of compact shielding system is also helpful for other new facility using this kind of BSA. Activation of Argon in the atmosphere and shielding material are also studied in this work.

Conceptual design of TRR medical room for BNCT

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The result of the first attempt to construction of a BNCT beam at Tehran Research Reactor (TRR) was presented in ICNCT-5 in 1992 by Dr. Pazirandeh. Nowadays, BNCT is under development at Tehran Research Reactor (TRR). Recent researches show that the thermal column of TRR is an appropriate facility which can be modified for epithermal BNCT. The main needed modification is to remove all graphite blocks from it but at present it is impossible. The most important challenge is the high gamma dose rate in the thermal column. The other alternative facility for BNCT is the TRR medical room. The medical room is located in the eastern part of the reactor pool structure. In order to use this facility for BNCT, it needs operation of the reactor core in the open pool position, and an in-pool BSA to guide neutrons to the medical room. In this work at first, an experimental and theoretical investigation of the use of this room for BNCT has been presented. The experimental investigation consists of (1) the possibility of operation of the reactor core in the open pool position, and (2) measurement of neutron energy spectrum near the eastern side of the reactor core. The theoretical investigation consists of MCNP Monte Carlo simulation to estimate the epithermal neutron flux at the patient position. Multi-foil activation method and SANDII unfolding code were used to measure the neutron energy spectrum. At the second part, the conceptual design of BNCT facility based on TRR medical room has been presented. The results show that in view of the technical aspects, the reactor core can operate in the open pool position. In an experiment the reactor core operate in this position for 20 min at 30 kW power. MCNP result shows that by considering a special in-pool BSA an appropriate epithermal neutron beam (~5×109 ncm-2s-1) could be achieved.

Neutron beam based on the nuclear reactors: using the experiences for accelerator-based BNCT

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Different efforts have been made during past 60 years in the world about using nuclear research reactors for BNCT and numerous clinical trials have been done which their result show the success of BNCT method. Now it is time to use this method as a routine cancer treatment method based on the use of in-hospital accelerator. The purpose of this work is a review on the different aspects of fission reactor-based BNCT facilities in the world wide including: the neutron beam design approaches, used materials in the beam lines, safety aspects, design tools and methods, etc. there are about 40 nuclear reactors which are investigated for BNCT such as MITR, BMRR, LVR-15, FiR-1, JRR-4, RA-3, RA-6, HFR, MUSASHI, KRR, WSU, MARIA, TAPIRO, HANARO, KUR, DIDO, MURR, BUTR, MTR, GTRR, IRT, YOYI, IJS, TRR, MNSR, etc. In addition, some aspects of accelerator based BNCT facilities which are under construction for in-hospital BNCT are presented and will discuss how we can use the reactor-based experience to develop the accelerator-based BNCT in the world.

^{124}SbBe photo-neutron source for BNCT: is it possible?

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Nuclear research reactors are the major neutron sources used in BNCT. At present, major efforts are underway to develop the in-hospital neutron source for BNCT such as proton accelerators. This paper presents an investigation on the use of SbBe photo-neutron source for in-hospital BNCT. In the Sb-Be neutron source, neutrons are formed from the interaction of the photons emitted from ^{124}Sb ($t_{1/2}$ = 60.2 days, E_γ = 1.691 MeV) with the Be through the photo-neutron reaction ^{9}Be (γ, n) ^{8}Be. Researches have been shown that this neutron source can be used as a mobile neutron source, and for neutron radiography. In comparison with other neutron sources, especially ^{252}Cf, this neutron source has two important advantages: (1) the source has effectively an on/off switching capability since the removal of the Be target would terminate the production of the neutrons; (2) it emits neutrons with mean energy of ~ 24 keV. These low energy neutrons can easily moderate to the epithermal neutron energy range which is suitable for BNCT. The main disadvantage of the source is its short half-life; however, it is always possible to "charge" the source up again by irradiation in a nuclear reactor. In order to obtain a proper neutron beam, a BSA has been designed using MCNP Monte Carlo code. to deliver 20 (Gy-eq) dose to a brain tumor in a reasonable time 500 kCi of ^{124}Sb is needed. This would be several hundred times the activity of a typical Cobalt radiotherapy source and issues with handling and security would be significant.

Advances in the autoradiography technique for Boron-10 quantification in bone

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Boron neutron capture therapy research is influenced by the latest advances in science and technology, which promote the increase of clinical scenarios that can be treated with this chemically targeted form of radiotherapy. One of those is osteosarcoma, an invasive limb tumor that is being investigated for clinical BNCT by several research groups worldwide.

One of the difficulties to study hard tissues for BNCT is the measurement of the boron concentration using nuclear techniques. Nuclear techniques commonly used to determine the boron concentration in soft tissue such as neutron autoradiography, require a calibration curve able to relate the boron concentration in the sample with the track density on the nuclear track detector.

The construction of a calibration curve involves generating samples with known amount of boron. These standards must have a structure similar to the sample to be measured and ensure a homogeneous distribution of generated tracks on the detector. In the case of hard tissue this is not a trivial task.

In previous works, bone powder was studied as a surrogate of the thin sections for neutron autoradiography. As a result, a preliminary calibration curve was successfully obtained. Due to the promising outcomes attained with this preliminary curve, an upgraded experiment including a refined scale of boron concentrations was designed and carried out.

Reference standards were constructed by soaking sheep femur powder in boric acid solutions ranging from 0 to 100 ppm. The final boron concentration of the standards was determined theoretically, assuming total water evaporation of the boric acid. After drying in a vacuum bell and placed in Lexan cases of 0.01 cm^3, the assemblies were exposed to a neutron fluence of 10^{12} n cm^{-2} at the thermal column of the RA-3 Reactor (Argentina).

After irradiation, an etching process with PEW solution (30 g KOH+80 g ethyl alcohol+90 g distilled water) at 70ºC revealed the latent tracks produced by the neutron capture of boron. These tracks were counted automatically using a microscope (CNEA-CONICET, Carl Zeiss MPM 800, 40x) and an image processing software (Image Pro Premier).

Samples with boron concentrations above 100 ppm presented numerous track overlaps causing an underestimation of the track density quantification. For this reason, several tracks images were

generated computationally and counted with the same image processing software of the experiment. The ratio between the number of generated tracks and the number of counted tracks was applied as a correction factor to the software-assisted counting. As a result, a linear relationship was found between tracks density and boron absorption in the samples. Thus, a robust calibration curve was constructed using these standards. Ongoing measurements of unknown boron containing samples will be compared with ICP-OES results in order to validate the technique.

3D SPECT reconstructed image from prompt gamma ray in BNCT for a heterogeneous human phantom: A Monte Carlo simulation study

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Introduction: To analyze the effects on three-dimensional single photon emission computed tomography (SPECT) image reconstructed by the 0.478-MeV prompt gamma rays for a heterogeneous human phantom in boron neutron capture therapy (BNCT) via Monte Carlo simulation.
Materials and Methods: The well-known Monte Carlo toolkit Geant4 and MCNP was used for the simulations. ICRP recommended materials were utilized in the simulation. A cubic phantom with soft tissue was used to study the prompt gamma emission during BNCT. The Chinese hybrid phantom with arbitrary tumors was constructed and used to acquire the 0.478-MeV prompt gamma rays in BNCT. Tomographic images were reconstructed with the iterative maximum likelihood expectation maximization (MLEM) algorithm.

Results: The emission rate of gamma rays in the soft tissue was basically same between MCNP and Geant4. Up to 30 kinds of gamma rays were found in the simulation, and the peak of 0.478-MeV prompt gamma ray was observed obviously, indicating the potential background of the SPECT system in BNCT. The single tumor with the diameter of 1 cm to 4 cm could be easily recognized from the reconstructed image with MLEM reconstruction method. At the same time, four tumors in the same patient were identified through the reconstructed image with MLEM. The multiple-field irradiation was proposed to improve the tumor dose distribution and increase the imaging quality.

Conclusion: The SPECT system for a heterogeneous phantom in BNCT was simulated with the Monte Carlo toolkit Geant4. With larger tumor size the attenuation of the neutron fluence results in the inhomogeneous distribution of the reaction rate (prompt gamma number) in the tumor target. Overall, the results show that the BNCT-SPECT is valid for the reconstruction of the boron capture interaction rate for heterogeneous patient.

The investigation for optimization of melanoma BNCT models in mice

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Boron neutron capture therapy (BNCT) is a tumor selective therapy that is based on the principle of preferential uptake of ^{10}B labelled compounds such as boronophenylalanine (BPA). ^{10}B is essential for BNCT to generate alpha particles of high energy by nuclear reaction. Besides BNCT system that utilizes nuclear reactor, accelerator-BNCT systems are being developed. The accelerator-BNCT system is expected to be installed in hospitals, where prompt gamma-ray analysis (PGA) that can be used for measurement of boron concentration at nuclear reactors is not available. Inductively coupled plasma atomic emission spectrometry (ICP-AES) is another useful method to evaluate boron concentration in the blood of patients. We have been investigating the strategies to optimize ICP-AES and evaluate the biological effects of BNCT on melanoma.

For this purpose, various human and mouse melanoma cell lines were analyzed for colony forming abilities, radiation responses, and mouse xenograft models. The measurement strategy of boron concentration in cells, tumors and blood in mouse models were also optimized using ICP-AES. Using male BALB/c *nu/nu* mice, the boron concentration in blood was measured after i.p. injection of BPA at 250 mg/kg bodyweight.

In the time-course study the boron concentration reached a maximum level at 60 min and then showed a gradual decrease. Among 10 analyzed cell lines, 5 cell lines showed colony forming abilities. Two cell lines, MeWo that has no BRAF mutation and A375 that harbors BRAF mutation showed tumorigenicity after subcutaneous injection of tumor cells in BALB/c *nu/nu* mice, respectively, and the preferential uptake of BPA. These results will be useful for optimizing the BNCT conditions for melanoma.

The DNA double-strand breaks damage in CHO cells Induced by the fractionated neutron irradiation

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Introduction

Boron neutron capture therapy (BNCT) is usually provided by one irradiation. However, when cancer has spread widely, like malignant pleural mesothelioma and liver tumor, it is necessary to fractionate the irradiation. In this study, the effect of fractionated irradiation of neutron beam on normal cells was studied by 53BP1 foci assay to detect the DNA double-strand breaks damage.

Materials and Methods

Kyoto University Research Reactor (KUR) heavy water facility and gamma ray irradiation system were used as experimental radiation equipment. CHO (Chinese Hamster Ovary) cell line was also used for this study. As the method of irradiation, fractionated irradiation and consecutive irradiation were conducted in both neutron beam and gamma ray. In case of fractionated neutron beam irradiation, the first irradiation of CHO cells in a Teflon tube was conducted with neutron beam. The CHO cells were cultured for 23 hours after the irradiation. The floating cells were rinsed by PBS before the second neutron irradiation.
Irradiated cells were incubated 3 h, and washed with cold PBS. After fixation with 3.6% formalin, immunofluorescence staining was performed. The foci number and foci size were analyzed using a fluorescence microscope (KEYENCE, BZ-9000) optional software and Image-J (NIH).

Results

The mean value of 53BP1 foci number induced by the fractionated neutron irradiation was reduced by 25% in comparison with single irradiation at the same dose. The mean value of 53BP1 foci number induced by the gamma-ray irradiation was reduced by 30% in comparison with single irradiation at the same dose.
The foci size of 53BP1 showed larger induced by fractionated neutron than gamma-ray irradiation. There was possibility that the unrepaired DNA damage is remaining and amplified due to high LET component in the neutron beam.

Conclusion

The unrepaired cluster DNA damage was higher detected following fractionated neutron irradiation than gamma-ray irradiation.

Gadolinium Neutron Capture Therapy for Brain Tumor Therapy: A Preliminary Evaluation

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The gadolinium (Gd) shows potential of companion theranostics. Firstly, Gd is a paramagnetic lanthanide that possesses a longitudinal relaxivity (r_1) of water proton for a particular contrast agent of T_1 magnetic resonance imaging (MRI). In addition to diagnostic function, Gd is feasible to participate in neutron capture therapy (NCT), triggered by thermal neutrons with isotopes of gadolinium. The gadolinium-157 (^{157}Gd) possessing 255000 barn of thermal neutron capture cross-section, is the most potent nuclide for neutron capture reaction in periodic table. Neutron capture reaction of ^{157}Gd is quite complicated because prompt gamma rays, soft x-rays, internal conversion (IC) electrons and Auger-Coster-Kronig (ACK) electrons are generated. Most importantly, IC electrons and ACK electrons are high linear energy transfer (LET) particle radiations, showing capability of killing cancer cells *in situ*. However, potential toxicity and specific targeting delivery of gadolinium remain challenging the gadolinium neutron capture therapy (GdNCT) for practical use of brain tumor therapy. In our study, efficacy for several Gd-containing species against GBM8401 and U87 human glioblastoma cell lines are evaluated by viability, cytotoxicity and colony formation assays. Applicable strategies and preliminary results of treating GBM8401-bearing mouse by GdNCT will be introduced in this presentation.

Effect of oxygen pressure during incubation with a ^{10}B-carrier on ^{10}B uptake capacity of cultured *p53 wild-type* and *mutated* tumor cells with reference to dependency on *p53 status* of tumor cells and types of ^{10}B-carriers

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Introduction

Evaluating the effect of oxygen pressure during incubation with a ^{10}B-carrier on ^{10}B uptake capacity of cultured *p53 wild*-type and *mutated* tumor cells.

Materials and Methods

Cultured human head and neck squamous cell carcinoma cell line transfected with mutant *TP53* (SAS/*mp53*), or with a *neo* vector as a control (SAS/*neo*) was incubated with *L-para-boronophenylalanine-^{10}B (BPA)* or *sodium mercaptoundecahydrododecaborate-^{10}B (BSH)* as a ^{10}B-carrier at the ^{10}B concentration of 60 *ppm* for 24 hours under aerobic (20.7 % of oxygen) or hypoxic (0.28 % of oxygen) conditions. Immediately after incubation, cultured tumor cells received reactor thermal neutron beams, and a cell survival assay was performed. ^{10}B concentration of cultured SAS/*neo* or SAS/*mp53* cells incubated under aerobic or hypoxic conditions was determined with a thermal neutron guide tube.

Results

Hypoxic incubation significantly decreased ^{10}B concentration of cultured cells with a clearer tendency observed following *BPA* than *BSH* treatment in both SAS/*neo* and SAS/*mp53* cells. In both tumor cells, the aerobic incubation with *BPA* produced significantly higher ^{10}B concentrations than with *BSH*. However, after the hypoxic incubation with *BPA*, the ^{10}B concentrations were significantly lower than those with *BSH*. The ^{10}B concentrations after aerobic incubation with *BPA* or *BSH* in SAS/*neo* were higher than in SAS/*mp53* tumor cells although not significantly. However, the ^{10}B concentrations after hypoxic incubation with *BPA* in SAS/*neo* tumor cells were lower than those in SAS/*mp53* tumor cells again without significant differences. Those after hypoxic incubation with *BSH* in both SAS/*neo* and SAS/*mp53* cells were almost the same each other. Following neutron beam irradiation, SAS/*mp53* cells showed significantly higher relative biological effectiveness values than SAS/*neo* cells because of the significantly lower radio-sensitivity of SAS/*mp53* to gamma-rays than SAS/*neo* cells.

Conclusion

Oxygen pressure during incubation with a ^{10}B-carrier had a critical impact on ^{10}B uptake of cultured tumor cells. In clinical boron neutron capture therapy (BNCT), *BPA* is always employed as a ^{10}B-carrier combined with or without *BSH*. The intratumor distribution of ^{10}B from *BPA* very much depends on the oxygen pressure in tumor tissues, especially when tumors consist of *p53-wild* type tumor cells. The finding that the ^{10}B uptake capacity of *p53* mutated

tumor cells was not dependent on oxygen pressure as much as *p53* wild-type tumor cells showed that BNCT was very promising for controlling *p53* mutated tumors with radio-resistance to gamma-rays.

Topical application of histamine gel would protect oral precancerous tissue from BNCT induced mucositis but would affect therapeutic effect on tumors: preliminary studies in an oral cancer model

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Introduction: Oral mucositis, characterized by breakdown of the oral mucosa and development of ulcerative lesions, is an important toxicity in cancer therapy. It decreases patients´ quality of life, increases cost of care and may lead to undesirable dose reductions or treatment breaks, with a negative effect on cancer prognosis. Nowadays, adequate treatment/prevention of oral mucositis is still an unmet medical need. The hamster cheek pouch is a widely accepted model of oral mucositis and oral cancer. In this model, we evidenced the therapeutic effect of BNCT on tumors. However, associated mucositis in precancerous tissue surrounding tumors led to dose limitations and favored tumor development. We demonstrated, for the first time, the radioprotective effect of subcutaneous histamine in BNCT-treated animals, employing BPA, without compromising BNCT therapeutic efficacy. However, subcutaneous injections of histamine caused local irritation. Searching for new histamine protocols that would improve its radioprotective effect, avoiding local irritation, without compromising BNCT therapeutic effect, the present study evaluates the local administration of histamine as a gel in BNCT-treated animals.

Materials and Methods: The DMBA-cancerized cheek pouches were exposed to: (A) BPA-BNCT + histamine in gel (1 mg/kg/day, topical application during 16 days starting the day before irradiation) (n=8); (B) BPA-BNCT without histamine (n=7). The animals were irradiated at RA-3 nuclear reactor, with 5.9±1.2 Gy mean absorbed dose to tumor and 2.6±0.4 Gy to precancerous tissue. The animals were followed during 1 month.

Results: **Toxicity**: the animals did not suffer any signs of irritation, pain or discomfort due to histamine treatment. **Mucositis in precancerous tissue:** peak mean mucositis score at 11 days was 3.7±1.0 for BPA-BNCT and 3.6±1.2 for BPA-BNCT-histamine. Histamine gel quickened the resolution of mucositis: at 21 days mean mucositis was 1.8±1.1 for BPA-BNCT-histamine vs. 2.6±0.9 for BPA-BNCT; at 28 days mean mucositis was 0.5±0.6 for BPA-BNCT-histamine vs. 2.0±1.2 for BPA-BNCT. Besides, BPA-BNCT hamsters spent a higher % of evaluation time-points with a score of ≥ grade 3 than BPA-BNCT-histamine hamsters (61% vs 45% respectively). Histamine gel reduced the incidence and area of necrosis, i.e. 43% of BPA-BNCT animals exhibited necrosis (3/7 animals), with a mean area of 28.2±16.6 mm^2, whereas only 13% of BPA-BNCT-histamine animals exhibited necrosis (1/8 animals), with a mean area of 14.9 mm^2. **Therapeutic effect of BNCT on tumors:** total tumor response was 83% for BPA-BNCT and 79% for BPA-BNCT-histamine. Although these percentages did not differ significantly, tumor complete remission was significantly reduced

in BPA-BNCT-histamine vs. BPA-BNCT (30% vs 63% respectively). Besides, non-responder tumors rose from 13% in BPA-BNCT to 21% in BPA-BNCT-histamine.

Conclusion: Histamine exhibited a protective effect against BNCT-induced mucositis in precancerous tissue in the hamster oral cancer model, but significantly compromised tumor complete remission. As we demonstrated the importance of histamine dose scheduling and duration of dosing in our previous BNCT experiments, further studies are needed to optimize the histamine gel protocol to achieve a significant protective effect against mucositis without compromising BNCT therapeutic effect on tumors. It is noteworthy that histamine gel is easy to apply, with no signs of discomfort.

Translational BNCT studies in the Hamster Cheek Pouch Model of Oral Cancer at the New Configuration of the RA-6 Nuclear Reactor

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Introduction: In 2001, at RA-6 we reported significant tumor control by BPA-BNCT in the hamster cheek pouch model of oral cancer. This very aggressive model, in terms of tumor development and radiosensitivity, is mainly used to evaluate the effect of BNCT on tumors. Next, we developed a less aggressive model of oral precancer that represents human precancerous tissue more closely and allows us to study the long term inhibitory effect of BNCT on the development of new tumors and associated mucositis in precancerous tissue. At RA-3 we demonstrated that BNCT inhibited tumor development, albeit associated to severe mucositis. Aiming to reduce mucositis in this oral precancer model, for the first time, we demonstrated that histamine reduced mucositis without compromising BNCT therapeutic effect. Nowadays, oral mucositis is a dose-limiting toxic effect in cancer therapy and its reduction represents an important unmet medical need. Between 2007 and 2011, RA-6 core configuration, fuel enrichment and power level were upgraded, as well as BNCT Beam´s performance by enhancing positioning capabilities and field uniformity. The aim of the present study was to assess the effect of BPA-BNCT in terms of mucositis in precancerous tissue and its therapeutic effect in the hamster model of oral cancer, at the new configuration of RA-6 versus the old configuration (2001). We also evaluated, for the first time in this aggressive oral cancer model, the radioprotective effect of histamine in precancerous tissue and its potential influence on the therapeutic effect of BNCT on tumors.

Materials and methods: DMBA-cancerized hamster cheek pouches were exposed to: 1) BPA-BNCT; 2) BPA- BNCT+histamine; 3) BO: Beam only; 4) BO+histamine; 5) CONTROL: cancerized, no treatment. Histamine was administrated subcutaneously over 5 days, 5 mg/kg/day in saline solution, starting one day before irradiation. Neutron fluence ($1{,}1x10^{12}$ neutrones/cm^2) was the same as in the old RA-6 configuration BNCT studies in 2001. The animals were followed during 1 month. The % of animals with severe mucositis and tumor response were analysed using Fisher´s exact test ($p<0.05$).

Results: BNCT induced severe mucositis. The incidence was slightly higher (albeit not significantly) than in the "old" configuration experiments (86% vs 67% respectively). BO induced low/moderate mucositis. Histamine slightly reduced severe mucositis induced by BPA-BNCT (75% vs 86%) and prevented mucositis altogether in BO animals. Tumor response was significantly higher in BNCT + histamine (96%) and BNCT (94%) versus BO + histamine (9%) ($p=0.0001$), BO (38%) ($p=0.0021$) and control groups (16%) ($p=0.0001$). BNCT tumor response did not differ significantly from the "old" configuration results (94%). Histamine did not compromise BNCT efficacy but did exhibit a tendency to reduce tumor response in BO animals.

Conclusion: Radiotoxicity and tumor control results at the "new" and "old" configurations of RA-6 were consistent. This is an important result in the context of the restart of the clinical and preclinical studies at the RA-6. Although we employed this overly aggressive cancer model, histamine exhibited a slight protective effect against mucositis without compromising BNCT therapeutic effect on tumors.

Development of Dual Formulations as Boron Neutron Capture Therapy Agents

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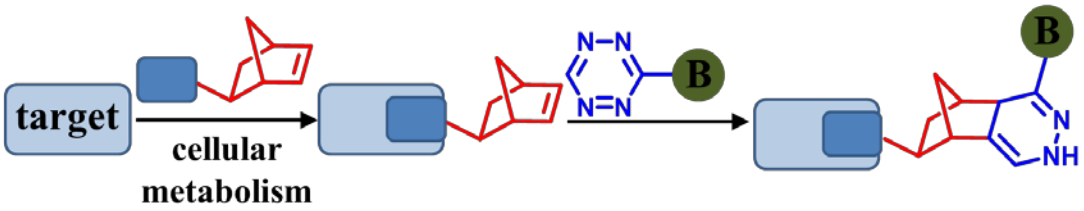
The emerging bioorthogonal reactions involve two reactive functional groups are highly chemoselective and unreactive to the other functionalities present in biological systems, and proceed in water at or near neutral pH, between 25 and 37 °C, also do not involve cytotoxic reagents or byproducts. Click chemistry, which plays very important role in bioorthogonal reactions, is generally applied only when a reaction meets several defining criteria: (1) modular, (2) wide in scope, (3) high yield, and (4) producing nontoxic or inoffensive byproducts. Orthogonal reactivity and concomitant application of click reactions have become critically important to a variety of fields, and click chemistries have already been demonstrated for functionalizing various biologicals, polymeric materials, surfaces, and inorganic nanomaterials. In this research, we will apply these conjugation techniques to develop dual formulations as boron agents for BNCT, e.g., conjugation of tumor targeting functional moiety and boron compounds with tetrazine ligation. Especially, Tetrazine cycloaddition with rapid kinetics and high specificity is a powerful tool for bioorthogonal reactions, and will play major role in this research. We will synthesize several norbornenes combined with hypoxia marker, folic acid, etc. for tetrazine Diels-Alder cycloaddition. Also, we will prepare various boron functionalized tetrazines for conjugation to functionalized tetrazines. The subsequent bioevaluation will be held with synthesized tetrazine-norbornene adducts, such as cell viability and evaluation uptake of adducts in tumors. The future objective of this dual formulations strategy is not only to apply practically on BNCT, but also have route-to-market, intellectual property, and integration of biotechnology and pharmaceutical industry.



Microdistribution and excretion pathways of boron neutron capture therapy agents delivered by rationally designed liposomes

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Matrix-assisted laser desorption ionization (MALDI) mass spectrometry imaging (MSI) for monitoring the microdistribution, circulation, and clearance of boron-containing Boron Neutron Capture Therapy (BNCT) agents, namely Na_3[1-(2′-$B_{10}H_9$)-2-$NH_3B_{10}H_8$] (TAC) and K[nido-7-$CH_3(CH_2)_{15}$-7,8-$C_2B_9H_{11}$] (MAC), was investigated. The goal of this study was to develop a rapid method for monitoring the boron content in the tissue so that an optimal neutron irradiation treatment window for BNCT can be determined. The analysis of distribution of boron agents in tumor tissue sections via MALDI-MSI has provided a visual confirmation that larger tumors retain boron agents in their peripheries while no boron agents were observed within necrotic tumor interiors. The co-localized presence of both TAC and MAC has also been visualized in sections of tumor, liver, spleen, and kidney tissues indicating that the boron agents primarily circulate in body within intact liposomes. Liquid chromatography mass spectrometry (LC/MS) analysis of samples of mouse urine and feces collected at different time points provided an insight into different clearance pathways of these agents. It was observed that TAC clears predominantly through urine while MAC clears through the bile duct. Structure elucidation of the MAC metabolites isolated from urine was carried out using Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometry and high resolution MS/MS fragmentation analysis.

Detection of Boron-Pharmaceuticals in Live Cancer Cells Using Fluorescent Boron-Sensor

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Since the study of interaction between boron compounds and biomolecules has been developed in recent years, boron-containing compounds are highly noted as a new class of pharmaceuticals such as *p*-boronophenylalanine (L-BPA, for boron-neutron capture therapy), Bortezomib (for the treatment of multiple myeloma) and Tavaborole (antifungal drug for onychomycosis).
To develop novel boron carrier for BNCT, it is necessary to elucidate the distribution of boron. Because, boron accumulation in the cell nucleus kills cells more efficiently during BNCT, grasp of the exact intracellular localization, distribution, and tumor/normal tissue ratio of boron pharmaceuticals are very important. The distribution of boron compounds in cells and biological tissues can be evaluated by detecting the boron atom present in boron compounds, because biological tissues contain little or no boron atom. However, most of the boron-detection methods such as ICP-OES and □-autoradiography require very expensive facilities and/or tedious pretreatments. Furthermore, these detection methods are not suitable for live cell imaging, the distribution of L-BPA in live tumor cell is not elucidated. Therefore, a convenient and affordable for the detection of boron is required.
Boron(III)-containing fluorescent dyes such as BODIPY is used in the various fields, e.g., chemicalbiology, analytical chemistry and material science. Generally, a boron(III) fluorescent dye has a heterocyclic structure which consists of boron(III) and *N*,*N*- or *N*,*O*- type chelating-ligand. In order to coordinate to the nitrogen and/or oxygen of such ligands, boron(III) stabilizes the ligand and renders the □-system planar. This complexation proceeds selectively and rapidly, and the resulting boron(III) complex fluoresces. Recently, a detection method of boric acids by using the chelating-ligand is reported. Above background led us to develop a method for evaluating the bio-distribution of boron pharmaceuticals using chelating-ligands as the fluorescent boron-sensor.
In the present study, we synthesized various fluorescent boron-sensors and elucidated the fluorescent property of the complex of boron-sensors and boron pharmaceuticals. Furthermore, we also report the convenient method for evaluating the *in vitro* distribution of boron pharmaceuticals using a boron-sensor.

Preparation and Evaluation of Complexes of Boric Acid and Hydrogen Fluoride for Boron Neutron Capture Therapy

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Hepatocellular carcinoma (HCC) is the most common type of liver cancer and is one of the most common cancers worldwide. While there are still no effective treatments for HCC unless it is diagnosed at early stage and resected before metastasis, boron neutron capture therapy (BNCT) may provide an alternative therapy for the treatment of HCC. Recently, Chou and coworkers have found that boric acid (BA) could be selectively accumulated at liver tumors and tumor vessels. The results show promise of BA-mediated BNCT for HCC. With the mechanism of BA uptake and interactions between BA and carbohydrates being currently under investigation, further conjugation of BA with fluorine-containing molecule or functional group is necessary to enable non-invasive evaluation of boron distribution by positron emission tomography (PET) with ^{18}F-labeled BA derivatives. On the other hand, such conjugation may partially or even completely change the chemical and physiological properties of such a small boron-containing molecule. In this study, we prepared complexes of BA (0.1 M) and hydrogen fluoride (HF) and evaluated their possible use for BNCT. Mixtures of BA and HF with varied HF/BA ratio of 1~4 were prepared in PBS and in serum, and the evolution of B-containing species was monitored by ^{11}B NMR. It was found that $[BF_3(OH)]^-$ was predominantly formed in both media at room temperature, and the anionic species gradually transformed to $[BF_4]^-$. With HF/BA = 3, the molar ratio of $[BF_4]^-$ and $[BF_3(OH)]^-$ increased from 0 upon mixing BA and HF in PBS to 1.5 after 2 h at room temperature. With HF/BA = 4, complete transformation of $[BF_3(OH)]^-$ to $[BF_4]^-$ was observed within 30 min at 70 °C. This suggests that $[BF_4]^-$ is the most stable species provided with sufficient amount of HF. Furthermore, thin-layer chromatography suggested similar affinity of $[BF_4]^-$ toward glucose, galactose, mannose and mannitol with that of BA. Cell uptake tests were also performed using HepG2 cell line in the media containing 150 ppm of BA or $[BF_4]^-$, and very similar uptake amounts were observed for the two boron-containing molecules. Further studies are in progress to examine the biosafety and biodistribution of $[BF_4]^-$ for its possible use for PET-BNCT.

Estimation of Radioactivation of Dental materials and Neutron Loss by Dental Materials, and the Measure for those problems.

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Radioactivation of elements which consist human body are already estimated. Therefore dental materials are not yet estimated well. In clinical dentistry, in order to maintain oral functions, dentist apply many kind of materials which contains many kind of elements which are not popular in human body. Also when NCT of head cervical area is applied, direction of neutron beam crosses dental devices in many case because head cervical and oral area are near.

The possible problems are: 1. Dental materials will be radioactivated by Neutron beam. It will increase exposure dose of patient. After NCT dentist may touch radioactivated dental devices, at that case contamination for environment may occur. 2. Dental materials may absorb neutron beam and may decrease strength of it than expected.

I have done estimation of radioactivation for 'dental cobalt chrome alloy', 'dental gold alloy' etc. For calculation, I used JDNEL-4.0 nuclear data. And found they cause problem with NCT.

And I have made 'Draft plan of measure for prevent dental material related problems in NCT'

1. Include dentist and dental hygienist to the NCT curing team.
2. Management plan for dental devices will be made by dentist.
3. Suspicious device should be removed before NCT. Changed to temporary devices which is made from materials not radioactivative. After NCT finished dental devices will be restored.
4. Also dentist consider swallowing function of patient after NCT.

Experimental study of uptake the boron compound in glioma stem cell

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Introduction

Glioblastoma multiform(GBM) is the most common malignant central nervous system primary tumor that has been incurable for decades. Tumor cells infiltrate into surrounding normal brain tissue, and in some cases, tumor cells have reached the contralateral hemisphere. It is difficult to remove all tumor cells by surgery without causing damage to normal brain functions. Recently, research showed that tumor stem cells caused recurrence of GBM. Glioma stem cells remain extremely resistant to all current forms of therapy including chemo and radio. Tumor stem cells have self-replication competence and differentiation into glioma cells. Though there have been no previous published reports about boron accumulation of glioma stem cells, the purpose of this study is to reveal boron kinetics in the tumor stem cell model.

Materials and Methods

Cell lines

TS cells and TSRR cells are GBM stem cells model of the mouse. TS cells are made from neural stem cells with genetic manipulation. TSRR cells are radio-resistance TS cells. These cells were cultured in D-MEM/F-12 medium and formed sphere. TS and TSRR cells were kindly purchased from Dr.Osuka, University of Keio.

Boron agents

This experiment was used two drugs, p-boronophenylalanine(BPA) and mercapto undecahydro-dodecaborate(BSH). BPA and BSH were prepared at a concentration of 60 μgB$_{10}$/mL.

Boron measuring

Each TS, TSRR and C6 cells were cultured in a medium with BPA or BSH. The solution of BPA and BSH were prepared at a concentration of 40 μg/mL. After a 1, 3, 6, 12, and 24-hour time lapse, the cells were treated with trypsin and PBS and the number of cells were measured. These cells were wet-ashed by using nitric and sulfuric acids. Boron concentration of these samples was measured using Inductively Coupled Plasma Atomic Emission Spectroscopy(ICP-AES).

Results and discussion

In 6 hours, BPA-TS was 0.426 +-0.0184 ppm/10^6cells, BPA-TSRR was 0.354 +-0.0636 ppm/10^6cells, and BPA-C6 was 0.250 +-0.0071 ppm/10^6cells.Also, in 6 hours, BSH-TS was 0.312 +-0.0225 ppm/10^6cells, BSH-TSRR was 0.365 +-0.0162 ppm/10^6cells, and BSH-C6 was 0.259 +-0.0460 ppm/10^6cells. The uptake of BPA and BSH was not related with culture time. There was not a big difference between boron concentration in TS, TSRR and C6 cells. In vitro, tumor stem cells can uptake boron as much as tumor cells.

Possible causes of these results are differences in cell form, sphere, and sheet. These results suggested that tumor stem cells are likely to uptake boron compounds as well as tumor cells. Furthermore, the nature of the stem cells is not lost.

Effects of the fast-neutron-rate in a neutron beam and the boron-density in a phantom on the RBE dose calculations for the accelerator-based BNCT

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For upgrading therapeutic beam performance for boron neutron capture therapy that adopts a small accelerator-based neutron source, a beam shaping assembly (BSA) that produces a neutron beam with a low fast-neutron-rate (FNR) and a low photon-rate in a high epithermal neutron flux is expected. However, accelerator-driven BSAs may be designed so as to be a high epithermal neutron flux rather than a low FNR, since the filtration necessary for dropping the FNR must greatly reduce the intensity of an epithermal neutron flux. The experimental investigations for the RBE dose in a phantom that is irradiated by various epithermal neutron beams from research reactors showed [1] that in-phantom figures of merit determined from the RBE dose varied with not only the FNR and the photon-rate in the epithermal neutron flux but also the ^{10}B-density in a phantom. We therefore performed simulation calculations using MCNPX to examine effects of the FNR and the boron-density on the RBE dose calculations.

We designed a BSA model that is based on ^{7}Li (p, n) reaction by 2.8 MeV protons in a beam current of 15 mA and produces a neutron beam having the recommended beam-characteristics shown in IAEA-TECDOC-1223, i.e. the FNR or the photon-rate in an epithermal neutron flux is 2×10^{-13} or 1.0×10^{-13} [Gy･cm^2]. Further, the BSA models having higher FNRs of 6×10^{-13} or 1×10^{-12} [Gy･cm^2] were designed for comparison. Then, the RBE dose in a phantom placed on a treatment position was calculated by the sum of boron dose, neutron dose, and photon dose , with the compound factors for the tumor and normal tissue of 3.8 and 1.3, with the RBE values for neutrons and photons of 3.2 and 1.0. In the calculation of the boron dose, ^{10}B-concentrations for the normal tissue and tumor (N and T) parametrically varied in many steps where the value of N changed from 2 ppm to 20 ppm and the value of T changed from (2xN) ppm to (10xN) ppm. We estimated the advantage depth (AD) that is the depth in the phantom where the RBE dose to tumor equals 10 Gy-eq and also the treatment time when the maximum of RBE dose to normal tissue becomes 10 Gy-eq.

Difference in the values of AD among the three FNRs was not so large, although 6×10^{-13} [Gy･cm^2] gave better results in general; somewhat larger values of AD for 6×10^{-13} [Gy･cm^2] than the others occurred in 49 % frequency in 170 combinations between the values of N and T. Longer treatment times occurred in cases of lower FNR with lower epithermal neutron flux, and in cases of lower N; the treatment time for the three FNRs was 2100, 1200 or 800 seconds when N equals 2 ppm, and was 1100, 700 or 600 seconds when N equals 20 ppm. These results suggest that accelerator-driven BSAs should be designed so that the FNR becomes somewhat higher than the recommended value by IAEA, especially when advanced compounds having low uptake in normal tissue and high uptake in tumor will be used.

[1] P. J. Binns, et.al, RADIATION RESEARCH 164 (2005) 212-220.

In-phantom gel dosimetry at TRR BNCT beam line

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The feasibility of the TRR as a neutron source for BNCT has been investigated and a suitable thermal neutron beam has been constructed recently. Completion of construction of the BNCT beam followed with the next step to perform dosimetry experiments. Nowadays, radiosensitive polymer gels are a reliable dosimetry tool for verification of 3D dose distributions. In order to obtain the three-dimensional (3D) dose distribution in TRR BNCT beam line, an N-isopropylacrylamide (NIPAM) gel has been produced using gelatin, NIPAM, N,N”-methylene-bis-acrylamide crosslinker and tetrakis (hydroxymethyl) phosphonium chloride antioxidant. To use the NIPAM gel, a head phantom has been constructed and filled with the NIPAM gel and irradiated in TRR BNCT beam line. Subsequently, the phantom containing gel was imaged by MR scanner, and then, the R2 maps were obtained by analyzing the MR images of the gel. Eventually, the dose distribution resulting from thermal neutron column of TRR were obtained with high resolution in 3D. The results show the potential of NIPAM gel for BNCT 3D dosimetry.

The effect of the moderator/reflector geometry of BSA on the skin dose during BNCT of brain tumours

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In order to provide an appropriate neutron beam for Boron Neutron Capture Therapy (BNCT), a special Beam Shaping Assembly (BSA) should be designed based on the neutron source specifications. In common BSA, the reflector is considered as a layer which covers the sides of the moderator materials. In this paper, the effect of some new proposed reflector/moderator geometries including multi-layer and hexagonal lattice on the skin dose during BNCT have been investigated. To do this a typical head phantom including ICRU 46 compositions has been used and all dose components have been calculated in the skin, skull and the brain tissues using MCNP4C Monte Carlo code. The watt fission neutron source has been considered in the calculations. The results show that the skin dose related to proposed multi-layer configuration is about 40% lower than the typical desired single layer geometry without any valuable change of treatment time.

Investigation on the BNCT for liver at TRR

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Recently, an appropriate epithermal neutron beam has been designed at Tehran Research Reactor (TRR). The main goal of this research is about investigation of using this beam for BNCT of the liver. To do this, the whole body MIRD phantom including the liver and a typical tumour has been used in MCNP4C Monte Carlo code and placed in the beam line and then four major dose components has been calculated in both normal and tumour tissues. The RBE factor for boron reaction has been set as 2.5 and 0.94 for tumour and normal tissues, respectively. Different boron concentration has been studied for both tumour and normal liver. The result show that the typical required time to deliver 20 Gy-eq dose to the tumour is about 40 min and the therapeutic gain, namely the tumour dose to maximum normal tissue dose is greater than 3.5 which is acceptable value.

A comparison of proton therapy and BNCT at TRR in treatment of brain tumors using the high-resolution voxel-based Zubal head phantom

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Particle therapy is a form of external beam radiotherapy using beams like protons or neutrons for cancer treatment. Protons show an increasing energy deposition with penetration distance leading to a maximum (the 'Bragg peak") near the end of range of the proton beam. This energy deposition can suffer the tumor. While in boron neutron capture therapy damage to tumors is mostly from energetic ions produced by the secondary nuclear reaction after the neutrons in the external beam are absorbed into boron-10 nuclide. In this study, there is a comparison between proton therapy and TRR BNCT neutron beam related to the side effect of these two therapy method. To do this, the high-resolution voxel-based Zubal head phantom has been used. The phantom consists of 25 brain structures and 15 different materials. For proton therapy, Catana facility (10nA) and for BNCT, TRR epithermal beam have been considered. The RBE factors for different radiation are used as following: gamma=1, proton=1.1, neutron=3.2 and boron=1.35 and 3.8 for normal and tumor tissues, respectively. a same irradiation geometry has been used for both BNCT and proton therapy. For proton dose +F6 MCNP card used and for BNCT, F4/DE4/DF4 cards considering appropriate KERMA functions have been used. The 18 and 65 ppm of 10B have been assumed in the tumor and normal tissues respectively. The results show that the treatment time to deliver 20 Gy-eq dose to a brain tumor is about 52 min in BNCT and 2 min in proton therapy. It also found that in BNCT, the Gy-eq dose to the other brain structures during treatment time is much higher than in proton therapy. In the other world, in BNCT, the side effect of treatment on the brain structures is very Significant in comparison to proton therapy. **Acknowledgement**: the authors would like to thank Dr. Sauli Savolainen, Dr. Sauerwein Wolfgang and also Dr. Finn Stecher-Rasmussen for their supports and their helps.

A new approach to use D-T neutron generator for BNCT

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There are some different works about using D-T neutron generators for BNCT. In that works, a typical Beam Shaping Assembly (BSA) was used to convert 14.1 MeV neutrons to an appropriate epithermal BNCT beam. In one of these works, natural uranium was used as a neutron multiplier which is need some safety regards and also has delayed gamma rays. In the present research, two new BSA configurations have been proposed and investigated. The proposed configurations are very different to common configuration and include multilayer and hexagonal lattice geometry. In multilayers geometry, there are some reflector layers and also some moderator layers which have been considered as every other layer. In lattice geometry, rod reflectors in different radius have been placed in the moderator material in hexagonal lattice geometry with different lattice pitches. The MCNP4C results show that these two suggested geometries are more effective than common geometry in reduction of thermal neutron flux. For example, in the multilayer geometry, the epithermal neutron flux can reaches to 5E9 n/cm2/s (considering the neutron source strength equal to 1.45e14 n/s) with acceptable values of fast and thermal neutrons and also gamma rays according to IAEA recommendation.

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Modern Arak heavy water research reactor for BNCT

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Todays, the only active neutron source in Iran that could be used for BNCT applications is the Tehran Research Reactor (TRR). There is no any advanced proton accelerator suitable for BNCT in Iran and so we need to have a plan to use the all available and existing facilities for research and development related to BNCT. Now, the most important available opportunity for the purpose is the re-design stage of Modern Arak Heavy Water Research Reactor (MAHWRR) and we have enough time to propose a full BNCT facility including the all required component. As the power of MAHWRR will be 20 MW, it is predictable that the reactor can provide an appropriate epithermal neutron flux. In this paper, the investigation about required changes in the old design of the reactor has been mentioned and discussed. As mentioned in the Joint Comprehensive Plan of Action (JCPOA) between Iran and the E3/EU+3 (article 7.3.6. in Annex III) about cooperation and scientific exchange in the field of nuclear science and technology including neutron capture therapy based on TRR and MAHWRR, it is another available opportunity for us to use the existing international experiences related to BNCT.

Dosimetric Impact Due To Intratreatment Positioning Error in Boron Neutron Capture Therapy for the High-Grade Glioma

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Purpose/Objective(s): Boron neutron-capture therapy (BNCT) needs extremely longer treatment time for neutron irradiation compared with conventional radiotherapy, such as photon, proton, and carbon ion therapy. For feasibility of long-time treatment, it is desirable to perform patient set-up so loosely and comfortably as to permit a bit of patient disposition in consideration of patient's fatigue. However, to the best of our knowledge, how much we can permit the deviation of irradiation field have not been fully elucidated from the viewpoint of therapeutically effective dose for treatment target. Now that we are eventually starting the first-in-the-world hospital-installed accelerator-based BNCT treatment in our institution, the study aimed to evaluate the dosimetric impact due to positioning error and intratreatment motion error in BNCT for the high-grade Glioma.

Methods and materials: This study was targeted for three patients that has the high-grade Glioma on their temporal lobe. First, based on Gd contrast-enhanced T1-weighted imaging (GdT1WI), tumor (GTV), brain stem, eye-lens, optic-nerve, and optic-chiasm were delineated, and dose calculations were performed with the radiation treatment planning system (SERA). The distance from a collimator to the patient's surface is different in every cases, but the suitable condition to achieve the best distance was selected. Now, we decide to name the plan of this calculations non-FLAIR plan. After calculations, the maximum, minimum, and mean dose for the GTV and some normal tissues were evaluated. Next, based on FLAIR-weighted imaging (FLAIRWI), the area of high signal intensity on FLAIR (FLAIR-high area) was delineated as FLAIR by additions. The dose calculations for this plan named FLAIR plan was performed, and some doses were evaluated in the same as before. Finally, in condition that the irradiation fields shifted 2, 5, 10 mm to the direction RL and ±2, 5, 10 mm to the direction SI in both non-FLAIR and FLAIR plan, dose calculations were performed and some doses were evaluated, respectively.

Results: For the deviation of irradiation field in the direction RL and SI, The mean dose (D50) and minimum dose for the GTV and the area of high signal intensity on FLAIR (FLAIR-high area) tend to become lower than in original treatment plan. The changes of the minimum dose for the FLAIR-high area were drastic compared to those for the GTV. As for the FLAIR-high area, the degrees of deviation in the direction of RL, AP, and SI that can compensate therapeutically effective dose for the FLAIR-high area were different for each patient. In some cases, even 5-mm deviation did not compensate therapeutically effective dose for the FLAIR-high area.

Conclusions: Intratreatment positioning error due to loose patient set-up has an impact on the dose quality especially for the area of high signal intensity on FLAIR that might include the infiltrated tumor cells, and in some cases makes the possibility of recurrence. Pretreatment evaluation for the degree of deviation that can compensate therapeutically effective dose should be performed in each patient.

Potential of NIPAM Polymer Gel in 3D Mapping of Dose Distribution in Shallow Brain Tumors Treated Using BNCT

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Introduction: Because of the unique characteristics of polymer gel dosimeters, it appears that these gels might offer a reliable method for measuring absorbed radiation dose from various radiotherapy techniques, such as BNCT. In this study, the ability of NIPAM polymer gel to record the dose distribution from the BNCT treatment modality was evaluated by simulating the clinical conditions for treatment of shallow tumors.

Methods and Materials: NIPAM gels both with and without the simulated tumor (the gel with ^{10}B) in polymethyl methacrylate (PMMA) cylindrical phantoms were irradiated using the BNCT beam of the Tehran research reactor (TRR).

Results: The results show that NIPAM gel can be used in neutron dosimetry, allowing the dose distribution in BNCT to be mapped in 3D.

Conclusions: It is concluded that NIPAM gel has the potential to be used in verification of BNCT treatment planning.

Development of the accelerator based Boron Neutron Capture Therapy system for cancer treatment within 1 hour therapeutic time

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An accelerator based BNCT(A-BNCT) system is under development with a goal to use practical cancer treatments within about 1 hour therapeutic time at a hospital in Korea. To meet the goal we have designed and developed a high power accelerator system and its target assembly to produce a high epithermal neutron flux of $2x10^9$ n/cm^2.S. It consists of 10MeV proton linear accelerator and 80kW beryllium (Be) target and moderator system und the considerations of deduction of residual gamma radiations and fast neutrons. This paper is focused on some details of design, engineering and construction of a practical epithermal neutron source for hospital based uses.

Design of a Beam Shaping Assembly for the Nagoya University BNCT Engineering Study System

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An electro-static accelerator with the maximum energy and current of 2.8MeV and 15 mA, respectively, is now under construction for a BNCT engineering study at Nagoya University in Japan. The aim of this facility is to examine engineering feasibility of a BNCT system using this accelerator. The proton energy is near the threshold energy of neutron production using Li or Be. At this energy the Li target gives much higher neutron intensity. Therefore, we decided to use Li as a target. A beam shaping assembly (BSA) will be different from the one designed for higher energy protons around more than 10MeV since the produced neutron energy is less than 1 MeV.

We performed design study of a BSA for a Li target BNCT system that fulfils all the conditions indicated in IAEA-TECDOC-1223 in order to obtain maximum epithermal neutron intensity. The IAEA-TECDOC conditions are as follows.

Epithermal neutron intensity>1.0×10^{9}n/sec/cm^2

Fast neutron rate < 2×10^{-13} Gy･cm^2

Gamma ray rate < 2×10^{-13} Gy･cm^2

Thermal neutron rate < 0.05 Current/Flux > 0.7

We started from a reference BSA designed for a proton energy around 10 MeV. The transport calculation was performed using PHIS code with ENDF/B-VII.1. MgF_2 is optimal as a moderator material at lower proton energies[1] and Pb is suitable for fast neutron reflector. However, due to the low neutron energy Fe-filter was removed since it is only effective to the neutrons with energies more than 1 MeV. First, the open area of a neutron extraction hole at the moderator side was widened within allowance of the Current/Flux. It gave more than 50% increase of epithermal neutron intensity. In this BSA gamma ray and thermal neutron doses are not so large, so we could reduce Bi and Cd thickness. Furthermore, we changed the position of Pb and LiF so as to attach Pb to the moderator. These change gave around 30% further gain in the intensity. Next, we re- designed rear part of the moderator. The fast neutron rate was reduced by adding MgF_2 around the proton beam hole adjacent to the moderator rear part. It allowed to use the thinner moderator and resulted in remarkable increase of the epithermal neutron intensity. At last we got about 2.5 times higher epithermal neutron intensity compared with the reference one, and the intensity was around 2×10^{9}n/sec/cm^2.

We are still continuing the optimal design study on the BSA taking into account various effects to be considered for the clinical treatment.

[1] Y. Hashimoto, F. Hiraga, Y. Kiyanagi, Physics Procedia, 60, 332-340(2014)

An Approach to be a General Radiation Therapy for BNCT

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Background and Purpose:

The opportunity of Boron Neutron Therapy (BNCT) is extended more likely by the realization of the accelerator BNCT irradiation system, and the possibility that BNCT becomes the general radiation therapy has come out. Social expectation has led a little too much, but, a big chance has come for the field of BNCT. It is suitable timing to consider what is effective way to make BNCT a general radiation therapy.

Approval of the Pharmaceutical Affairs Law is indispensable to make a general radiation therapy. The approval examination has been carried out based on regulatory science. When this standard is indicated precisely, BNCT which extremely has difficulty in scientific dose evaluation for the individual patient during BNCT has little way to be approved.

The physical absorbed dose distribution for the individual patient in the BNCT treatment is not clarified, so, the relations with curative effect and the side effect is not clear. There is a big reason that the absorbed dose of BNCT caused by the reaction between boron-10 atoms and thermal neutrons. In other words, there is no evaluation of the boron concentration distribution and its time dependency in the tumor cell and normal cell during BNCT.

Approach 1:

According to the social role of scientists, researchers and engineers, i.e. open, fare, honest, we should disclosure the limit of dose of radioactivity evaluation in BNCT of the individual patient, and get the understanding of the person concerned.

Present BNCT has evaluated a neutron exposure dose, curative effect and the side effect in the protocol which is established using average data provided through much fundamental experiment and clinical studies for a boron compound dosage method. For the present exposure dose evaluating system, we have been used the CBE coefficient that estimate the uptake mechanism to the tumor of the boron compound, and prior boron concentration distribution data by the PET image analysis using 18F-BPA. However, the absorbed dose evaluation at the cell level in the BNCT treatment is impossible.

Approach 2:

It is to realize a measuring method which can estimate absorbed dose distribution at an affected part and the neighboring during BNCT treatment in tissue organ level.

Of course, even if this kind of measurement method is established, we cannot say enough. However, we could make helpful situation to get the understanding of the person concerned, because an absorbed dose and relations of the curative effect could be clear than present dose estimation.

A new production method for patient fixing implement by combination with a three-dimensional printing technique and treatment planning system

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Introduction

In irradiation for boron neutron capture therapy (BNCT), positioning and immobilizing for a patient is very important because patient's move in irradiation affect doses to tumor region and around organs at risks. In conventional procedure for the BNCT, patient is led to the irradiation position by using some lasers in irradiation room, and is fixed softly by using cushions and bandages. However, the patient moves easily during irradiation in particular for the irradiation for head-and-neck cancer. Thus patient have to keep the position without move while irradiation. Based on this situation, we have invented a new production method for patient fixing implement by combination with a three-dimensional (3D) printing technique and "Tsukuba plan" as a treatment planning system. Production methods for a human body or several organs by using 3D printing technique have been already established. However, a distinct feature of the method is that the method enables to produce directly a fixing implement including complicated shape like outline of a face by using polyethylene with lithium fluoride (PE with LiF) as a neutron shielding material. The material has proven to be applied to shielding for organs at risks like eyes in BNCT.

Materials and methods

First, we design shape for the implement along patient's outline in each CT image for a patient by using Tsukuba plan. The treatment planning system outputs the data including the implement shape by DICOM format. And we have also developed a tool which can covert the DICOM into 3D CAD data automatically. Thus, a mold for the implement is created based on the 3D CAD data outputted from the tool. The mold is made of silicon rubber compound. An optimum amount of micro-pellets for the PE with LiF as a raw material for the implement is poured into the mold and packed by vacuuming cavity in the mold. We have employed electromagnetic wave fabrication method as the 3D printing technique to form the material. Finally, by the microwave external irradiation to the mold involving the micro-pellets, the implement including outline of the face is produced easily and precisely.

Results and discussions

The method enables to form directly an implement including complicated outline of a patient's body by using PE with LiF. The implement helps not only for immobilization of the patient while irradiation but also for positioning to irradiation position before irradiation. Moreover, the implement made of PE with LiF can be used to neutron shielding and irradiation field control against several healthy organs by adding shielding parts for their regions on the implement body. Details for the production procedure and advantages for the production method are presented in the congress.

Induced Radioactivity and Residual Dose Rates in a Boron Neutron Capture Therapy Facility Based on Be(p,n) Reaction with 30 MeV Protons

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A scoping analysis of material activation at a proposed accelerator-based boron neutron capture therapy (BNCT) facility in Taiwan was performed, aiming to estimate the magnitude of the problem related to induced radioactivity and residual dose rates under worst case assumptions. The basic layout of the facility included an accelerator room and a patient treatment room. The epithermal neutron beam for BNCT purpose was generated by coupling a neutron production target with a specially designed beam shaping assembly (BSA), which was embedded in the partition wall between the two rooms. Neutrons were produced from a beryllium target bombarded by 1-mA 30-MeV protons. Operation of such a high current accelerator will produce intense secondary neutrons and result in serious material activation. The FLUKA Monte Carlo code was used to estimate the production and decay of radionuclides after nuclear interactions induced by primary and secondary particles. Following the generation and transport of decay radiation, the space- and time-dependent inventories of induced radionuclides in materials and residual dose rates after shutdown were obtained. The beryllium target and BSA were the main concern of material activation because of direction proton bombardment and intense neutron irradiation, respectively. The analysis of induced radionuclides in surrounding concrete was also conducted. Two simplified operation scenarios were assumed in this study: a 30-minute proton bombardment to simulate a typical shift of patient treatment and a long-term 1-year continuous operation to estimate the accumulation of long-lived radionuclides.

A comparison of dose distributions in GTV between BNCT alone and combined BNCT-IMRT treatment planning for head and neck cancer

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Introduction

Since 2014 we had a protocol of combined BNCT and IG-IMRT for recurrent head and neck (H&N) cancer. Aim of this study are utilize IMRT photon dose to compensate dose heterogeneity in BNCT alone planning and evaluate planning quality indices of simulated IMRT plus BNCT combined planning versus BNCT planning alone.

Materials and methods

Five patients with recurrent H&N cancer received CT simulation according to the Taipei Veterans General hospital (TVGH)'s standard protocol for BNCT in 5 mm slice thickness. These patients treated BNCT in Tsing-Hua Open pool reactor (THOR) by using THORplan3.0 treatment planning system (TPS). After BNCT, we utilized the same CT images to calculate photon IMRT TPS in Eclipse13.0 with Monte Carlo calculation algorithm. The gross tumor volume (GTV) was delineated by an experienced oncologist according to the ^{18}F-BPA PET or MRI image. In BNCT planning, a single field was set forward to cover GTV with the shortest depth by CT image. The prescribed dose is 18 Gy-Eq receive 80% volume to the GTV in a single fraction. All IMRT plans were generated using the Eclipse treatment planning system with AAA algorithm. A simulated dose of 56 Gy to the GTV in 20 fractions with 6 step and shoot IMRT fields was planned. The plans were created for a 6 MV photon beam Varian clinic ix® linear accelerator with an Millennium 120 MLCs. Optimization was performed to get the best plan for each technique for each individual patient and BNCT plan as the based plan before IMRT optimization. We evaluated planning quality indices including conformity index (CI) and homogeneity index (HI) for GTV in BNCT and combined IMRT-BNCT planning. HI was also calculated in IMRT planning for GTV.

Results

Mean volume of GTV is 120.5 cm^3. In IMRT plan, the mean monitor unit and beam on time are 953 MU and 1.56 minutes in total 6 fields. The CIs for GTV were 0.74 and 1.13 in BNCT and IMRT-BNCT combined planning. The HIs for GTV were 2.3, 2.33 and 1.23 in BNCT, IMRT and IMRT-BNCT combined planning, respectively.

Conclusion

Combined BNCT-IMRT planning can obtain better dose distribution in GTV than BNCT alone. Dose inhomogeneity in IMRT may impair its biological effect in daily treatment.

A bi-tapered and air-gapped beam shaping assembly used for AB-BNCT

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The $^{7}Li(p,n)^{7}Be$ reaction, leads to a relatively soft yielded neutron spectrum, is often chosen as the neutron- producing reaction for AB-BNCT. This study aims to design a compact beam-shaping assembly and auxiliary systems for the $^{7}Li(p,n)^{7}Be$ reaction-based neutron source, and to evaluate the relationship between the BSA design and the consequent neutron beam quality for a further optimization.

A proton beam of 2.5 MeV with 10 mA was used in this study. For the sake of simplicity, only one moderator material, AlF_3, was considered in the BSA design. Criteria of the epithermal neutron flux, fast neutron and gamma-ray contaminations, thermal-to-epithermal neutron flux ratio and neutron current-to- flux ratio listed in the IAEA-TECDOC-1223 report were used to evaluate the free-in-air figure of merit. In addition, the dosimetric performance in the modified Snyder phantom was examined to evaluate the beam line quality in treatment.

On the premise that the size of moderators and the induced fast neutron contaminations were comparable, a bi-tapered design can increase the beam intensity by 80% and 5% when compared to a typical cylinder and a single-tapered BSA, respectively. When an air gap was integrated into the designed model, the beam intensity was further raised by 10% of that in the single-tapered model and the gamma-ray contamination was decreased by about one third. In the dosimetry evaluation, the use of the bi-tapered and air-gapped BSA can get a weighted absorbed dose to tumor greater than 65 w-Gy within 30 minutes of irradiation. The 30 w-Gy treatable depth and the advantage depth were beyond 7.5 cm and 10.5 cm in phantom, respectively, which indicated a great penetrability of the neutron beam.

As a result, the beam shaping assembly with a bi-tapered and air-gapped design could generate a high- intensity epithermal neutron beam, reaching 140% of the IAEA recommendation. Also, the dosimetric performance in the modified Snyder phantom shows the proposed BSA can treat tumor with a depth deeper than 7 cm and the treatment time is less than 30 minutes.

Extension Collimator designed and used for BNCT clinical trial at THOR

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In order to retain the possibility of treating large tumors, the beam field size of a neutron beam used for boron neutron capture therapy (BNCT) is typically much larger than the target tumor volume. How to adjust the field size to meet the target tumor, and how to overcome the positioning problem raised by the shoulder, were two issues when use the Tsing Hua Open-pool Reactor (THOR) for BNCT treatment of recurrent head and neck cancer.

In this article, we will share the experience of the extension collimator designed and used for BNCT clinical trial at THOR. The effectiveness of the extension collimator was based on MCNP simulation results. They were compared with various materials composition, various thicknesses of the extension collimator, various sizes of the rear opening, and even different collimator's shapes. According to the MCNP simulation results, the adding of the extension collimator will soften the neutron spectrum and reduce the neutron intensity simultaneously. This will cause the required irradiation time becomes long while delivering the same thermal neutron fluence to the target tumor. Besides, the simulation results also show that Li-Poly is an ideal material for making extension collimator. The appropriate total length of the extension collimator is in the range of 10~15cm, and the size of the rear opening should depends on the dimension of the target tumor.

In addition to the traditional conical shape, we also investigate the feasibility of a neutron multi-leaf collimator for BNCT treatment. Preliminary results show that neutron multi-leaf collimator can effectively change the neutron beam profile at the beam exit, thereby reducing the risk of critical organ doses received.

Using Lithium-6 Filter for Study of Dose Distribution with Maximum and Minimum Displacement of Prostate inside the Body in BNCT Method

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Abstract

Boron neutron capture therapy (BNCT) is an ideal method to kill prostate cancer cells without harming the healthy cells around the tumor. Investigation the physical dose of prostate tumor and nearby healthy tissues have been done for ORNL, adult male (AM) and KTMAN-2 phantoms using Monte Carlo transport code. Two different spectra of MIT reactor (without and with lithium filter) were considered. To evaluate the effectiveness of this method for killing cancer cells at different prostate depths, the prostates were moved three times in an interval of 3cm toward the surface of the body. In addition, the effects of using different thicknesses of lithium filter on the physical doses of prostate and nearby healthy tissues were examined. It is observed that by decreasing the depth in which prostate is located, the physical dose received by tumor increases. When the prostate is seated at the maximum depth inside the body, tissues located in the beam path receive the maximum amount of dose. However, using the lithium filter, the damage to healthy tissues reduces, as when prostate is near the body surface, the lithium filter increases the amount of dose delivered to the tumors. In this situation, mean energy of the epithermal neutron and neutron penetration distance in the tissues increases. By changing the location of prostate gland inside the body, physical doses of the normal tissues do not change, but it was observed that increasing the lithium filter thickness causes a significant reduction in normal tissues doses.

Keywords: MIT neutron spectrum, BNCT, Prostate tumor, Lithium-6 filter, Voxel phantoms

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Development of Treatment Planning System for in-hospital BNCT system

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Clinical trials of BNCT employing a cyclotoron based neutron source on recurrent malignant glioma and recurrent head and neck cancer are currently underway in Japan. In order for BNCT to be commercialized and spread as a general purpose treatment option, medical device approval is necessary for a BNCT Treatment Planning System (BNCT-TPS). Sumitomo Heavy Industries is currently developing SACRA planning, a commercial BNCT Treatment Planning System (TPS) for hospitals.

The following features are desired in a BNCT-TPS:

1. Ability to run on a general purpose workstation
2. A DICOM interface for patients' images and plan data
3. Target volume contouring based on F-BPA PET images
4. Fast dose calculator based on Monte Carlo method
5. Plan evaluation tools such as dose and DVH viewers
6. User-friendly interface for operators

SACRA planning runs on a windows workstation. Patient's image of CT, PET, MRI and fusion images are supported. Accordingly, contouring of target volumes using F-BPA PET images to assist in plan determination is possible. We implemented the dose calculator based on PHITS, which is a multi-particle Monte Carlo transport code developed by JAEA. And, dose calculator can compute dose distribution and neutron fluence in 3-D voxel models based on patient images and ROIs. Plan evaluation tools include the ability to display main and supplementary dose distribution and DVH. In this presentation, our development BNCT-TPS are introduced.

Estimation for exposure dose to medical workers in an accelerator-based BNCT system with a Li target

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Introduction

With operations of an accelerator-based BNCT system, the interaction of proton beams with the target generates neutrons. The neutrons are transported to each equipment of the system and are slowed down in it. This would result in activation of the moderator and its surrounding structural materials. Therefore, it is required to protect medical workers against radiation exposure from radionuclides induced by the neutrons. We estimated the effective dose from the radionuclides to the medical workers before/after irradiation of the neutrons by Monte Carlo simulation. The result was compared to the effective dose limit for the medical workers recommended by the ICRP Publication 103.

Materials and Methods

The D-chain code and T-track code in the Particle and Heavy Ion Transport code System (PHITS ver.2.73) were used for the Monte Carlo simulation. Nuclear data such as half-lives, gamma-ray energies and branching ratios of the radionuclides were referred to the National Nuclear Data Center (NNDC). Six parts (moderator/moderator cover/reflector/boron shield/Steel special Use Stainless (SUS) cover/silicon cover) were selected as the activated subject. Mean effective dose for 20 min per irradiation at a representative evaluation point was calculated by using the effective dose conversion coefficients of photons for the anterior-posterior (AP) geometry. The evaluation point was set at a distance of 0.8 m in the vertical direction from the center of the irradiation aperture with an offset of 0.6 m in the lateral direction. The duration time the medical workers stay at the evaluation point was set to 20 min: 10 min before the irradiation and 10 min after 5 min past from the completion. The total number of the irradiations were set to 1040 times per year (4 times/d×5 d/w×52 w/y). The effective dose per year was obtained by multiplying the mean effective dose per irradiation by the total number of the irradiations.

Results

The effective dose at the evaluation point was 34.19 mSv/y. The contributions from ^{20}F ($T_{1/2}$ =11 s) in the moderator and ^{56}Mn ($T_{1/2}$=2.58 h) in the SUS cover were dominant. Replacing the SUS cover with that of Steel structure (SS), the effective dose at the same point was reduced to 0.26 mSv/y, and thus, the effective dose limit for the medical workers (20 mSv/y) was satisfied because the SS cover doesn't contain manganese.

Conclusions

The effective dose to the medical workers from the moderator and its structural materials being subject to activation in our system was estimated by using PHITS. It was recommended that the SS be used for the structural material in order to reduce the effective dose caused by activation, and we found it would satisfy the effective dose limit for the medical workers recommended by the ICRP Publication 103.

Monte Carlo simulation of depth–dose distribution in brain model for boron neutron capture therapy

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Introduction: Boron Neutron Capture Therapy (BNCT) is a biologically targeted, binary radiation therapy for cancer which combines neutron irradiation with a tumor targeting agent labeled with a stable isotope of boron having a high thermal neutron capture cross section. Absorbed dose delivered to the normal tissue and tumor during BNCT result from possible reactions from three types of directing ionizing radiations with different LET characteristics such as $^{14}N(n,p)^{14}C$, $^{10}B(n,\alpha)^{7}Li$, $^{1}H(n,\gamma)^{2}H$, $^{1}H(n,n)^{1}H$ and all of (n,γ) reactions due to neutron activation of elements. Determination of total absorbed dose required complex calculations because the neutron and gamma rays in the normal tissue and tumor cells have an energy distribution. All of the calculations were carried out using the Monte Carlo MCNPcode.

Materials & Methods: The neutron beam based on the $^{7}Li(p,n)^{7}Be$ reaction, with 2.3 MeV proton energy and 10mA current, was considered as the primary neutron source. A modified Snyder head phantom was considered as a representation of a patient head, the elemental compositions for material of the phantom: scalp, skull and brain have been taken from ICRU 46. The head was positioned at the exit side of the BSA. The absorbed dose from Heavy Charged Particles (HCP) was computed from the neutron flux generated by MCNP for each cell tally in Head phantom. The weighted total dose is defined as the sum of physical dose components multiplied by the weighting-factors of each dose component in a tissue; the ^{10}B concentrations were assumed to be 52.5 ppm for tumor and 15 ppm for healthy tissue, and the CBEs/RBEs were 1.3 and 3.8 for boron dose in healthy tissue and tumor, respectively, 3.2 for the 14N(n,p)14C reaction and 3.2 for elastic scattering in hydrogen.

Results: The advantage depth (AD), one of the important dosimetric properties used to evaluate the ability of neutron beam to treat deep-seated tumors, was also calculated. It was found that the maximum dose can be delivered at 3.4cm depth in head with a dose rate of 0,519 RBE Gy per minute. The dose ratio, of tumor to normal tissue, of 4.92 can be obtained.

Discussion & Conclusions: In this study, By means of numerical simulations, the RBE dose has been calculated and the beam quality was also characterized with the help of the dose estimation in the Snyder's head phantom.
The results showed good treatment possibilities with short irradiation times. The beam penetration is good: maximum tumor dose at 3.4cm depth; and an advantage depth of 9.2 cm. with the maximized dose ratio 4.92 of tumor to normal tissue. So, we can treat tumors in the biggest range of depth and shorter treatment times with good therapeutic ratio.

Development of a moderator-based spherical neutron detector for BNCT

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The neutron field used in BNCT has a continuous energy spectrum, which has a neutron energy peak near 1 keV with an intensity of approximately 1.5×10^9 (n/cm^2/s). However, on-line methods for measuring the neutron spectrum of the BNCT neutron field have not been developed yet. Hence we have developed a moderated-based spherical neutron detector with a ^{3}He detector.

In this study, in order to optimize the material composition and size of the moderator spheres of the detector, calculations were carried out using the Monte Carlo code MCNP5 with the cross section set: ENDF/B-Ⅶ. As a result, we have adopted fluoride-containing bonner spheres. Because the fluorine has a low neutron absorption cross section around a few keV, sensitivity of the detector in energy region increases and resultantly the detector is suitable for the BNCT neutron field. Finally, the neutron response functions of the detector were obtained by the MCNP5 calculation.

To validate the performance of this neutron detector, the response functions were measured at the monochromatic neutron irradiation field in the Facility of Radiation Standards (FRS) of the Japan Atomic Energy Agency. In the measurement, the monochromatic 8 keV- and 26 keV-neutrons were generated by using a nuclear reaction of Sc(p,n), and 250 keV- and 565 keV-neutrons by Li(p,n) reaction. For the sphere with a diameter of 12.08 cm, the ratios of calculation / experiment (C/E) of response functions with neutron energy of 8 keV, 26 keV, 250 keV and 565 keV are 0.88, 0.89, 0.72 and 0.96, respectively. On the other hand, for that with a diameter of 15.08 cm, the ratios of C/E of response functions with those neutron energies are 0.83, 0.94, 0.82 and 0.99, respectively. The comparison shows that the calculation agrees well with the experimental results within about 15%, except for 250 keV.

In future, we will conduct an experiment to verify the applicability of the detector in a BNCT neutron field for the practical use.

Preclinical Studies to Optimize the Application of Boron Neutron Capture Therapy (BNCT) for Treatment the Superficial Cancer

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Introduction: BNCT is a cancerous, cells selective, non-conventional radiotherapy modality to treat malignant tumors. It is based on a nuclear reaction B-10(n, □) Li-7. The Argentine clinical facility located at the RA-6 Research Reactor (Bariloche Atomic Center) developed a neutron beam for BNCT on superficial tumors called "Hyperthermal".

Because of the characteristics of this neutron beam, the maximum thermal flux is 1cm deep, the total absorbed dose in superficial tumors such as melanoma is lower in the first millimeters than in the center of the tumor. Some materials (eg. Silver, Rhodium and Indium) have the ability to capture neutrons and emit high energy beta radiation. Thin foils of these materials, named Enhancers Beta (BE) could be used to compensate the irradiation over the tumor and even increase the local total dose during a conventional BNCT treatment. Our goal was to evaluate the toxicity and effectiveness of BE devices as a complementary tool for BNCT.

Materials and Methods: NIH nude mice 6-8 weeks of age were implanted subcutaneously into the right rear flank with 10^6 cells of a human colon cancer cell line (ARO) developed from 15 days post injection, tumors between 50 and 100 mm^3. Thirty animals were divided into 5 groups: a) Control; b) NCT: neutron irradiation (without BPA); c) Rhodium BE + NCT (without BPA); d) BNCT: BPA 350 mg / Kg; e) BNCT + Rhodium BE. To adapt the neutron beam for BNCT patients small animals reflector / neutron scattering was placed. The animals were irradiated in a specific position for 37 minutes with a flow in tumor $4.96x10^8$ n/cm^2.seg. Mice were anesthetized with a combination of diazepam (40mg / kg) and ketamine (200mg / kg) administered both subcutaneously with a period of 20 min each. Post irradiation animal weight, tumor volume growth and further histological studies of tumor and surrounding normal tissues evaluated were performed.

Results: The post irradiation monitoring of animals did not report any sign of radiotoxicity in the treatment volume and the surrounding normal tissues. The tumor growth curves versus time showed significant differences between the groups c, d and e (NCT + BE; BNCT; BNCT + BE) compared to groups 1 and 2 (Control; NCT) ($p<0.05$).

Conclusions: These preliminary results show that BE devices do not induce radiotoxicity and could be used in BNCT to optimize therapy.

Pilot studies to evaluate the effectiveness of high LET particle irradiation in damaging neurotoxic protein aggregates

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A growing number of diseases, namely amyloidosis, are associated to an abnormal production or reduced clearance of proteins assuming insoluble aggregated structures which deposit in the intra- and extracellular brain compartments. Alzheimer's disease (AD) is one of the most frequent amyloidosis where Aβ aggregates deposited in the brain as senile plaques. The Aβ peptide results as the culprit of the neuropathological process. The aging of the world population foreseen for the next decades is expected to increase AD and other dementia incidence, implying both a higher number of patients in need of caregiver's assistance and huge socio-economical costs. These prospects heighten the concern about the lack of therapeutic tools able to significantly slow down the disease progression.

In the late 1990's, the effectiveness of External Beam Radiation Therapy (EBRT) in the treatment of localized TracheoBronchial Amyloidosis (TBA) was described suggesting its application to AD. The mechanism by which EBRT affects TBA is unclear. A phyisico-chemical process of Aβ aggregates depolymerization by low dose, long term fractionated radiotherapy was hypothesized. This mechanism is DNA-independent and a very low dose per fraction regimen, with an extended overall irradiation period, is suggested to match the brain tolerable dose. Presently only one *in vitro* study, using high doses of low LET radiation (5-20 Gy of photons) has been reported showing extremely poor differences between irradiated and sham Aβ aggregates. More recently an *in vivo* study carried out on a transgenic murine AD model has shown a significant reduction of senile plaques and improvement in cognition performances after the delivery of a clinically relevant course of external beam irradiation.

Pilot studies started recently at Pavia University to evaluate the effectiveness of high LET particles irradiation in damaging protein aggregates. Water solutions of aggregated Bovine Serum Albumin (used as reference) and Aβ were irradiated using standard α and β sources (Am-241; Sr-90/Y-90) as well as inside the thermal column of Pavia research nuclear reactor, after having enriched the protein solution with ^{10}B and ^{157}Gd-vectors.

The irradiation set-up specifically developed for these tests will be described, together with the preliminary dose calculations and the first outcomes obtained by comparing irradiated and non-irradiated protein solutions.

Evaluation of BSH containing Kojic acid (KA-BSH) as a novel agent for boron neutron capture therapy

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Introduction: Kojic Acid (KA) is obtained from mushrooms that are native to Japan and is also a by-product of the fermentation process used to produce the alcoholic beverage *sake*. KA was originally discovered in 1989. Since then the substance has been used widely in skin care products, especially for lightening skin pigmentation because KA interacts with the melanogenesis process and melanin production by inhibition of tyrosinase. To develop practical materials utilizing boron-10 (^{10}B) carriers, we previously designed, synthesized and evaluated various BSH containing compounds. Among them, BSH containing KA (KA-BSH) was found to be a promising compound capable of delivering higher concentrations of ^{10}B to various tumors as well as melanoma. In this study we evaluated the effect of the novel ^{10}B carrier KA-BSH in a rat brain tumor model.

Materials and Methods: Biodistribution studies were performed in Fischer rats bearing intracerebral implants of F98 rat glioma cells. KA-BSH was administered by means of intravenous injection in 3 doses (10, 20, 30 μg^{10}B/kg). Animals were euthanized at different time points (1 and 3 hours after termination) and tissues were removed for boron determination by ICP-AES. In addition, intracellular distribution of KA-BSH in F98 cells was examined by immunochemical staining. BNCT was performed at the Kyoto University Research Reactor Institute (KURRI) using KA-BSH 1 hour after intravenous administration.

Results: The tumor boron concentrations showed the highest concentrations at a dose of 30μg^{10}B/kg 1 hour after termination; the boron concentrations at a dose of 10, 20, and 30μg^{10}B/kg were 1.42 ± 0.28, 2.96 ± 0.74, and 6.65 ± 0.25 μg^{10}B/g, respectively. The corresponding normal brain concentrations were low (0.25, 0.34 and 0.50μg^{10}B /g, respectively). Immunochemical staining of F98 cells showed that KA-BSH was incorporated into the cell membrane of the F98 cells and aggregated on the fringe of the cell nuclei. Median survival times (MST) of untreated and irradiated control rats were 29.5 and 30.5 days, respectively, while animals that received KA-BSH, followed by BNCT, had a MST of 36.0 days (p=0.0027, 0.0053).

Conclusion: Use of the novel KA-BSH compound in BNCT was effective in prolonging MST in a rat malignant glioma model, in spite of a low tumor distribution. One explanation may involve a tendency for higher intracellular accumulation of KA-BSH. Immunochemical staining showed different intracellular distribution for each compound, therefore it can be expected that use of KA-BSH in combination with BPA may have a further curative effect. Based on these findings, KA-BSH is promising new boron compound for malignant glioma.

Abscopal Effect of BNCT

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Introduction. The Abscopal effect would inhibit tumor growth at a site distant from the primary site of radiotherapy. Localized standard radiotherapy has been shown to induce abscopal effects in several types of cancer. The biologic characteristics underlying this effect are not completely understood, but it may be mediated by immunologic mechanisms. The fact that the beneficial effects of radiation might extend beyond direct cytotoxicity to tumor cells could be used to advantage in oncological therapy. The aim of the present study was to evaluate, for the first time, the potential Abscopal effect of BNCT. **Materials and Methods.** Twenty-six BDIX rats were inoculated subcutaneously with $1x10^6$ DHD/K12/TRb syngeneic colon cancer cells in the right hind flank. Three weeks post-inoculation, the animals developed measurable, vascularized tumor nodules. Twelve tumor-bearing rats were injected with BPA intravenously (46.5 mg ^{10}B/kg). The right leg bearing the tumor nodule was locally irradiated 3 h post-administration of BPA at RA-3, using a $^6Li_2CO_3$ shielding, prescribing a maximum absorbed dose of 7.8 Gy to skin as the dose-limiting tissue. An additional group of 14 tumor bearing rats were left untreated and used as control. Two weeks post-BNCT, $1x10^6$ DHD/K12/TRb cells were injected subcutaneously in the contralateral left hind flank of each of the 26 BDIX rats. Tumor volume in the right leg was determined employing a caliper, pre-BNCT and once a week post-BNCT for 7 weeks in BNCT treated and untreated animals. Likewise, tumor volume was measured weekly in the contralateral left flank to assess a potential influence of the response of BNCT treated tumors in the right leg on tumor development in the left leg. This potential inhibitory effect on tumor development in the left leg, induced by a positive response to BNCT of the tumor in the right leg, was used as an indicator of Abscopal effect of BNCT. Clinical signs and local toxicity were monitored throughout. The end of the follow-up period was established at 7 weeks post-BNCT, based on excessive growth of the tumors in the right leg of untreated animals. **Results.** Tumor volume in the left leg was smaller (albeit not significantly) in animals treated with BNCT in the right leg, than in untreated animals (164 ± 163 mm^3, n=12 vs 254 ± 251 mm^3, n=14 respectively). Within the BNCT group, a statistically significant reduction was observed in left tumor volume in animals whose right leg tumor responded to BNCT (post-treatment/pre-treatment tumor volume<1) vs animals who failed to respond (post/pre ≥ 1), i.e. 13 ± 15 mm^3, n=5 vs 271 ± 251 mm^3, n=7 (Student´s t test, p=0.0013). In addition, a statistically significant reduction in left leg tumor volume was observed in BNCT-responsive animals versus untreated animals, i.e. 13 ± 15mm^3, n=5 vs 254 ± 251 mm^3, n=14 respectively (p=0.05). The only sign of radiotoxicity was moist desquamation in exposed skin. **Conclusion.** The present study, albeit preliminary and performed in a simple animal model, provides proof of principle that the response of a tumor to BNCT is capable of inducing an Abscopal effect.

L-Phenylalanine preloading reduces the $^{10}B(n,\alpha)^{7}Li$ dose to the normal brain by inhibiting the uptake of L-BPA

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Boron neutron capture therapy (BNCT) is a cellular-level particle radiation therapy that combines the selective delivery of boron compounds to tumor tissue with neutron irradiation. The boron compounds commonly used for BNCT, dihydroxy-borylphenylalanine (L-BPA), is a good boron compound for glioblastoma and head and neck cancer in clinical settings. However, the tumor selectivity of L-BPA is not ideal, yet. Several BNCT studies have described ways to enhance tumor uptake of L-BPA or to decrease the relative accumulation of L- BPA in normal tissue, such as the concomitant use of other substances with L-BPA, and the optimization of the L-BPA prescription dose. Previously, GM Morris *et al*. found that the compound biological effectiveness (CBE) factors of L-BPA for the central nervous system depended on the injection dosage. They found that high dose L-BPA injection protocol (blood boron concentration: 93 ppm) had lower CBE factor than low dose L-BPA injection one (blood boron concentration: 19 ppm). This result is very promising for reducing adverse effects of BNCT on the central nervous system. However, injection of a high dose of L-BPA, as much as 1600 mg/kg L- BPA injection, is not feasible in clinical settings. Based on their report, we have analyzed CBE factors for radiation myelopathy and found that CBE factors are not influenced by the boron concentrations in the blood, but by the boron concentration ratio of the normal tissue to the blood (N/B ratio). In this study, we aimed to find an alternative method for high dose L-BPA injection to improve the therapeutic efficacy of BNCT. We examined the effects of oral preloading with various substrates (1000 mg/kg) of L-type amino acid transporters, the transporters of L-BPA, in a xenograft tumor model and found that high-dose L-Phenylalanine reduced the accumulation of L-BPA especially in the normal brain relative to tumor tissue. Then, the effect of preloading with various concentrations of L-Phenylalanine (50, 100, 250, 500, 1250, and 2500 mg/kg in 1ml of water) before L-BPA injection on L-BPA accumulation in tissues was examined. We found that the dose-dependent beneficial effects of L-Phenylalanine on N/B ratio of the normal brain. The N/B ratios of 1250 mg/kg and 2500 mg/kg L-Phenylalanine groups were significantly decreased relative to that of the control group ($p < 0.01$). As a result, the maximum irradiation dose in the normal brain was 19.2% lower in the high-dose L-phenylalanine group relative to the control group. This study provides a simple strategy to improve the therapeutic efficacy of conventional boron compounds for BNCT for brain tumors.

Property and in vitro study of a liposome modified boron lipid for combination therapy

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[Introduction]

An estimate of ^{10}B concentration needs at least 20-30 μg in tumor tissue (g) for BNCT. However, the candidate compound which achieved necessary boron concentration didn't satisfy other condition (low toxicity, high solution and the low distribution in the normal organization). Therefore we developed the boron liposome for combination therapy (BNCT and chemotherapy) to get higher antitumor effect.

Recently, liposome as DDS material is remarkable for EPR effect that the drug accumulate to tumor. EPR effect is caused by material to control physicochemical property (particle size, surface potential, etc.).

We investigated the effect of encapsulated doxorubicin in boron liposome which we already developed for BNCT.

[Material and Methods]

Novel boron lipid (PBL) and other lipids (Distearoylphosphocholine, Cholesterol, DSPE-PEG) prepared using the constant ratio were dissolved in organic solvent (chloroform, methanol) using the conventional lipid-film method. The resulting liposomes were extruded with an extruder through a polycarbonate membrane with a 100-nm pour size, yielding the liposome.

The liposomes encapsulating doxorubicin were prepared following the pH-loading method and measured inclusion ratio by fluorescence spectrometry. The cytotoxic effect of boron liposome encapsulated doxorubicin were measured by WST assay. We evaluated the efficacy of in vitro by use of CT26 (mouse colon carcinoma cell) and RAW264.7 (mouse macrophage cell).

[Results and Conclusion]

1) Higher inclusion ratio of doxorubicin were obtained by changing the lipid composition ratio.
2) A long blood circulation time were expected by effect of boron liposome on the experiment using these cell line.

[Acknowledgements]

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Development of *closo*-Dodecaborate-Serum Albumin Conjugates via Ruthenium-Photocatalyzed Tyrosine Modification for Neutron Capture Therapy

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Albumin, a native and major component of blood, is a considerably safer drug carrier than other artificial nanoparticles. Since albumin was found to be accumulated into tumor through, so-called, enhanced permeability and retention (EPR) effect, much attention has been focused on the development of albumin-based drug carriers. For example, Abraxane®, an albumin-paclitaxel nanoparticle reducing cytotoxic of paclitaxel, is the most advanced drug delivery product first approved by FDA in 2005 for the treatment of metastatic breast cancer. Furthermore, albumin microspheres have been investigated in controlled release systems as vehicles for delivery of therapeutic agents to local sites.

In the previous study, we chose a maleimide as a functional group to conjugate with bovine serum albumin (BSA) and synthesized a maleimide containing *closo*-dodecaborate (MID). MID covalently bound to both lysine and cysteine residues of BSA under neutral conditions and the resulting MID-albumin conjugates were selectively accumulated into tumor.

On the other hand, we have recently developed a technology for tyrosine residue-selective chemical modification of proteins. We have already found that tyrosine residues of BSA were labeled with tyrosyl radical trapping regents (TRTs) which contain *N*'-acyl-*N*,*N*-dimethyl-1,4-phenylenediamine moiety. TRT forms a stable C-C bond with tyrosine residues under visible light-irradiated conditions in the presence of photocatalyst, such as $Ru(bpy)_3Cl_2$. In this paper, we designed and synthesized the TRT-conjugated *closo*-dodecaborate (TRT-DB). We succeeded in the introduction of *closo*-dodecaborates at nucleophilic amino acid residues using MID and at tyrosine residues using TRT-DB for development of highly boronated albumin carriers. The detailed preparation protocols and biological evaluation will be presented.

Synthesis of water-dispersible boron nitride nano-sheets for BNCT

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BNCT employs ^{10}B-pharmaceuticals administered for the treatment of malignancies and several aggressive cancers. The main requirement for this therapy is selective targeting of tumor cells by sufficient quantities of ^{10}B atoms required for their capture/irradiation with low energy thermal neutrons. Boron Nitride Nano-Sheets (BNNSs) have been considered to be possible candidates as a boron agent for BNCT because of its ultrahigh surface area and easy surface functionalization and especially their high boron density (ca. 50%) equivalents to hundreds to thousands per each Nano-Sheet. In the present study, we have reported for the first time the synthesis of BNNSs as carriers of boron atoms to overcome this problem and enhance the selective targeting and ablative efficacy of BNCT for tumors. A facile and efficient method has been developed to produce high yield BNNSs by a combined strategy of quenching pre-heated hexagonal boron nitride (h-BN) in an aqueous solution and subsequent liquid exfoliation. The thermal and quenching stresses promoted the exfoliation of h-BN into BNNSs and subsequent sonication of the pre-stressed h-BN led to formation of BNNSs with a thickness of less than 2 nm comprising of two to three layers that was confirmed by Atomic Force Microscopy (AFM) measurements. The presence of hydroxyl groups was confirmed by means of XPS and FTIR on the surface. Hydroxyl groups significantly improve the solubility of the BNNSs in aqueous media and more functionalization to add targeting properties. Restoration of the sp^2 honeycomb network and exfoliation of BN sheets were confirmed by UV-visible spectroscopy and XRD. The SEM and TEM investigations of the resultant BNNSs showed the structure and the sheet-like morphology of BNNSs. Therefore, we believe that this structure may serve as new promising material for future biological and medical applications.

Synthesis of Fluorescein-Tagged and Water-Soluble Carborane-Appended Compounds

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Current research in boron neutron capture therapy (BNCT) focuses on the synthesis of novel compounds with high boron conent as well as methods for their delivery into the tumor cell. For BNCT applications, the water-solubility of such boron-containing compounds must be resolved through chemical modification. Thus, water-solubility is highly desireable for biological evaluation and can be accomplished through decapitation of the carborane cage moetiy. Additionally, a fluorescent tag can allow the observation of their cellular uptake during biodistriubtion studies. Accordingly, several selected biomolecules and fluorescein were conjugated with iodinated *o*-carborane and characterized using Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (NMR), elemental analysis, and mass spectrometry (MS).

BNCT Antitumor Effect of Boron Nitride Nanotubes

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Carbon nanotubes (CNTs) have been attracting growing interest due to their unique properties including peculiar shape, nanoscaled size, high thermal stability, and excellent conductivity. These superb mechanical and electronic properties have made them very promising new applications in chemistry and physics, particularly for the development of new nanotechnologies. CNTs have also been studied for application as a drug delivery carrier in biological systems. Especially, the functionalized CNTs with a range of 100–300 nm length escape from uptake by the reticuloendothelial system, revealing longer blood circulation times. Like CNTs, Boron nitride nanotubes (BNNTs) are currently attracting wide attention in the scientific community. BNNTs were first discovered in 1995. BNNTs are structural analogues of CNTs, in which carbon atoms are fully substituted by alternating boron and nitrogen atoms, and possess advantages over carbon nanotubes: electrical insulating property and thermal and chemical stability. Furthermore, BNNTs are lightweight, have excellent mechanical properties, a stronger resistance to oxidation than carbon nanotubes, and biocompatibility, offering a multifunctional material in nanocomposite materials, nanoscale electrical devices, biomedical fields, optical systems, and promising space radiation shielding applications. Meanwhile, BNNTs have been considered to be possible candidates as a boron agent for BNCT because of their high boron density (ca. ~50%) equivalents to hundreds to thousands per each nanotube. However, their poor solubility in aqueous solutions is a serious problem for biological experiments. We found that the use of DSPE-PEG2000 was effective for preparation of the BNNT-suspended aqueous solution. BNNT–DSPEPEG2000 complexes accumulated in B16 melanoma cells approximately three times higher than BSH. We demonstrated the first BNCT antitumor effects of BNNTs toward B16 melanoma cells: the higher BNCT antitumor effect was observed in the cells treated with BNNT– DSPE-PEG2000 complexes compared to those treated with BSH. The detailed BNCT antitumor effect and the possibility of BNNT as a boron delivery vehicle for BNCT will be presented.

Neutron penetration profile in tissue like phantoms with different neutron energies

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Among other aspects like selective boron enrichment or cellular internalization of boron containing compounds, the density of neutron flux in deeper tissue regions is immanent for the yield of ionizing radiation due to BNCT reactions and thus the therapeutic potential of the respective BNCT approach. Therefore, we developed a 3D phantom which reflects physiological properties in terms of chemical composition, especially for the most neutron interfering elements hydrogen and nitrogen. Systematic irradiation experiments on these polysaccharide phantoms at the Heinz Maier-Leibnitz Zentrum POLI: Polarized hot neutron diffractometer (http://dx.doi.org/10.17815/jlsrf-1-22), have been preceded. Those experiments were evaluated with respect to former studies at the PGAA Prompt Gamma Activation Analysis Instrument (http://dx.doi.org/10.17815/jlsrf-1-46) at the same reactor. The fundamental difference between those neutron sources lays in their energetic profile possessing 1.83 meV (6.7 Å) for the PGAA instrument and 1.14 Å, 0.9 Å and 0.55 Å for the POLI instrument, respectively.
It could be clearly demonstrated that a strict wavelength dependent penetration capacity was observable which was also dependent on the composition of the deployed polysaccharide phantoms. In addition to that, phantoms were placed behind a rabbit skull, in order to simulate beam attenuation of POLI´s white beam caused by bone material.
Penetration depth evaluations are useful and necessary to predict the outcome of subsequent *in vitro* experiments on biological samples.

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How Boron Neutron Capture Therapy and other Innovative Therapies can be Game Changers in Palliative Care

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Patients with no more standard treatment options are often relegated to supportive care or palliative services, where emphasis is placed on improving quality of life and not prolongation of life. Hope may be provided to these patients in the form of innovative therapy, which can be defined as treatment used in cases in which standard treatment is believed to be ineffective. How we can reconcile these seemingly contradictory approaches will involve a two-pronged strategy. Firstly, we have to be aware that for patients who are deemed incurable, there is a changing paradigm to turn these into chronic diseases, where therapies are aimed at long-term control. Secondly, medical tourism is the other already occurring paradigm shift in patient management where patients travel abroad to seek treatment. By partnering medical tourism and innovative therapies, patients can enjoy quality time on a nice vacation while trying for a chance to prolong their survival. We attempt to illustrate this idea with BNCT; and propose a system that may be utilized to achieve a win-win situation for patients, institutions, research and maybe even economy.

Boron neutron capture therapy for multiple liver metastases: A case report

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Introduction: Chemotherapy is a standard therapy for multiple live metastases. There is no effective treatment option for chemo-refractory multiple liver metastases. Whole liver irradiation has been used for palliation of painful primary and metastatic liver diseases. Boron neutron capture therapy (BNCT) can deposit large dose gradient between cancer cells and normal cells. However, whole liver BNCT with curative intent is difficult due to inadequate thermal neutron distribution in the deep-seated liver tumors. In palliative situation, one-fraction BNCT for multiple liver metastases may have potential to be a treatment option. In this article, we reported BNCT for multiple liver metastases to alleviate pain and fullness in right upper abdomen.

Patient: A 55 year-old man with thymic carcinoma, left pleural tumors and multiple liver metastases had received systemic chemotherapy and intra-arterial chemo-embolization therapy for multiple liver metastases. Proton therapy had been applied to the left pleural tumors causing left back pain. He suffered from abdominal discomfort due to chemo-refractory enlarging liver tumors in 3 months. He referred to our center for further treatment of multiple and invasive liver tumors with BNCT.

Results: An ^{18}F-BPA-PET study conducted before BNCT showed accumulation of BPA in the tumor, with a tumor to blood (T/B) ratio of 2.7. The BNCT for the tumors mainly located in the left lobe was performed with an anterior epithermal neutron beam collimated with a 23 x 22 cm square collimator. The irradiation time, 45 minutes, was determined according to the dose constraint for whole liver. In this case, it was difficult to demarcate normal liver tissues from the tumors diffusely growing in the left lobe. Dose constraint was set to 5.0 Gy-Eq as a mean dose for whole liver including the tumor and normal liver tissues. The dose delivered to the tumors located in the left lobe ranged from 10 to 50 Gy-eq. Deep seated tumors or the tumors in the right lobe received the dose ranging from 0 to 10 Gy-Eq. The dose delivered to the tumors located in the left lobe ranged from 10 to 50 Gy-Eq. Deep seated tumors or the tumors in the right lobe received the dose ranging from 0 to 10 Gy-Eq. He experienced gastric pain for a week after BNCT. Gastric pain was treated with H2 blocker. In blood chemistry test, the values for AST and ALT elevated to 3.9 and 4.8 times higher values than those for upper limit of normal at two days after BNCT, respectively. These values returned to normal within 20 days after BNCT. In blood chemistry test, the amylase remained within normal range. Follow-up CT at 4.5 months after the BNCT revealed decrease in size of the tumors located in the left lobe. In blood chemistry test, the values for ALP and g-GTP decreased within 50 days after BNCT.

Conclusion: BNCT has potential to be a treatment option for palliation of pain or abdominal fullness caused by multiple liver metastases.

A study for the improvement of a thermal neutron irradiation equipment for BNCT researches at Kyoto University Reactor – An installation of beam monitor system

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Introduction

An irradiation rail equipment is used as the equipment for thermal neutron irradiation at Heavy Water Neutron Irradiation Facility of Kyoto University Reactor. The improvement of this equipment is considered as it is highly employed recently. As a part of this improvement, an installation of beam monitor is planned. At present, the dose estimation is performed by gold-activation method for thermal neutron and thermo-luminescent dosimeter for gamma ray. Accordingly, the dose estimation requires much labor, and time lag occurs before the estimation results are obtained.

Then, the beam monitor system is installed for the automatic and on-line systematization in the dose estimation. The beam monitor system consists of three different kinds of chambers. These respective chambers are sensitive mainly to thermal neutron, fast neutron and gamma ray. Each dose component can be discriminated by comparison of the response between these chambers. A study for the installation of the beam monitor system is reported.

Materials and Methods

Multi-Ionization Chamber System was applied for this study, which was developed by our group. For the thermal-neutron chamber, Si_3N_4 wall and N_2 gas were selected for the enhancement effect due to the (n,p) reaction of thermal neutron and nitrogen. For the fast-neutron chamber, polyethylene wall and CH4 gas were selected for the enhancement effect due to the elastic scatter of fast neutron and hydrogen. For the gamma-ray chamber, graphite wall and CO_2 gas were selected for the response suppression to neutron. The simulations for the arrangement of the chambers were performed using a Monte Carlo Code, PHITS. The response change of each chamber for the putting place, and the perturbation due to an irradiated sample were confirmed.

Results

The thermal neutron flux detected by thermal-neutron and gamma-ray chambers decreased at 10-cm backward from the normal irradiation position. The total deposit- energy of each charged particle depended on the total flux for the different arrangement. When the irradiated sample was placed, the thermal-neutron and gamma-ray fluxes increased due to the scatter and (n,γ) reaction. The thermal neutron flux increased about 2.4% due to the scatter by the sample. Similarly, each charged particle increased for the placement of the sample at thermal-neutron chamber. However, the total deposit-energy of proton decreased for the thermal-neutron chamber.

Conclusion

The simulation calculations were performed for the response changes of the ionization chambers in two situations. The total deposit energy of each charged particle was dependent on the total flux, but that of proton was independent for the thermal-neutron chamber, whether or not an irradiated sample was placed. The further simulations are required for the optimization of the chamber-system arrangement.

Conceptual design of an accelerator based neutron source for BNCT and other applications

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An accelerator-based BNCT project at Granada, Spain is being considered. This, the first BNCT project in Spain, is based on the production of epithermal neutron beams suitable for different clinical and research applications from a versatile high current proton/deuteron low energy electrostatic accelerator that will be developed as an upgrade of one of the existing machines.

In this talk the conceptual design of the facility will be presented, as well as the main parameters of operation. Different applications that will be pursued for preclinical and clinical research in BNCT and related disciplines will be mentioned. Preliminary results from Monte Carlo simulations will be shown.

Tailoring of an epithermal neutron beam for the RFQ-based facility of INFN

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Introduction: The Italian National Institute of Nuclear Physics (INFN) developed and realized a Radio Frequency Quadrupole (RFQ) proton accelerator. This machine is of interest to BNCT for the delivery of 5 MeV protons with 30 mA current in a Continuous Wave (CW) mode, able to produce a high intensity neutron source from the reaction $^{9}Be(p,n)^{9}B$. It was shown, that with an appropriate Beam Shaping Assembly (BSA) this accelerator can ensure an in air thermal neutron flux of $4.3 \cdot 10^{9}$ cm^{-2} s^{-1}. Such a neutron beam is suitable to treat shallow cancers like skin melanoma. To treat deep seated tumours, epithermal neutrons are needed. From the experience of the various groups treating especially brain tumours, the optimal neutron energy was set around 10 keV. However, more recent studies based on treatment planning simulations using CT scans of real patients affected by lung tumours demonstrated that for such deep-seated cancers the ideal energy is peaked towards 1 keV. The same holds for knee osteosarcoma. In this work the tailoring of an epithermal neutron beam with energy spectrum around 1 keV at the RFQ facility is presented.

Materials and Methods: The design has been performed by MCNP simulation; the neutron source was generated using experimental neutron spectra measurements. Different BSA configurations were analyzed both from the point of view of their physical parameters (compared to the suggested IAEA-TECDOC values) and from the point of view of their performance in the treatment of a real osteosarcoma.

Results: A clinically performing epithermal neutron beam was tailored from the INFN RFQ facility, providing an epithermal flux of $2.8 \cdot 10^{9}$ cm^{-2}s^{-1} and a fast neutron and gamma contamination respectively of $8.9 \cdot 10^{-13}$ Gy cm^{2} and $3.7 \cdot 10^{-13}$ Gy cm^{2}. This was achieved by using a bulk layer of aluminium fluoride (35.5 cm) enclosed in 2 layers of lithium fluoride of 0.5 cm each finalized with titanium and bismuth layer. The reflecting material surrounding the neutron source was chosen to be aluminium fluoride, while the shielding is filled with lead. The entire BSA is then coated with a 3 cm layer of lithium carbonate while externally to the beam there is a 15 cm layer of graphite.

Conclusion: What emerges, is that the evaluation of the figure of merit related to the physical parameters are not exhaustive for the evaluation of an epithermal beam for clinical BNCT. Work by MS. Herrera et al. showed similar results. Therefore, the IAEA-TECDOC guidelines for the tailoring of a BNCT beam should be taken as a reference to reach a good quality, but the dosimetric assessment on realistic clinical scenarios are a more powerful tool to choose a

configuration. In particular beams that do not strictly comply with these requirements may provide advantageous dosimetry in clinical application. This highlights the necessity to develop other methods for epithermal beam evaluation, a possibility may be to probe the tailored beam on standardized clinical cases. Recent international collaborations have been established in order to compare the performances of different beams, based on reactors and/or accelerators, following these criteria.

A new model for the determination of the biological dose in BNCT: weighted kerma factors and the LQ model.

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Currently in BNCT the equivalent dose is calculated as a sum of weighted doses with energy independent weighting factors obtained from Glioblastoma experimental data. We propose to determine the biological effective dose from the RBE of neutron-induced charged particles. This can be done with newly defined factors in two different ways: i) weighted kerma factors that take into account the biological effect of each interaction process as well as the neutron energy, if the neutron spectral fluence is known; ii) biological effectiveness weighting factors, if the physical dose components are known. In both cases, our model uses the linear quadratic model for the gamma component of the biological effective dose.

Moreover at present, the equivalent dose in BNCT includes the biological effect and it is directly identified to the reference photon dose in order to obtain the equivalent photon dose. We propose to use the linear quadratic model for the determination of the photon equivalent dose producing the same biological effect.

In our model the biological effective dose can be identified with non-fractioned and fractioned photon treatments, therefore it is possible to take advantage of the large clinical experience of fractioning treatments. We applied the model to some treatments and the results suggest a possible increment in the delivered dose in BNCT without reaching the limit in the reference photon dose. In order to confirm our results, survival studies have to be performed. We will show preliminary results of the experiments carried out at CNA (Spain) with epithermal neutron beam and with thermal neutron beam at ILL (France).

Thermal scattering libraries and their impact on neutron transport for BNCT dosimetry: experimental assessments.

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Dosimetry calculations for BNCT with Monte Carlo N-Particle (MCNP) tipically take into account, for any organic tissue, the thermal scattering treatment for hydrogen bound in bulk water. However, in these tissues, hydrogen is also present in macromolecules (protein, lipids, etc.) and in confined water. In previous studies with the MCNP code we have determined that the differences in thermal neutron flux calculations using libraries for hydrogen in polyethylene or hydrogen in water, in phantoms of adipose tissue, can reach values of 9%, depending on the type of source and irradiated geometry.

In order to confirm these results, reaction rates measurements were performed with a set of activation wires in phantoms, in three BNCT facilities: the thermal BNCT facility at the TRIGA reactor in Pavia (Italy), the epithermal beam of the RA-6 reactor in Bariloche (Argentina), and the thermal facility at RA-3 reactor in Buenos Aires (Argentina). In the cases of TRIGA and RA-3 reactors, two phantoms were studied in each facility, one composed of water and the other composed of fatty tissue. In the case of RA-6 reactor, two phantoms were considered, one composed of paraffin and the other composed of fatty tissue. The experimental results were compared with simulations performed with MCNP6, using two thermal treatments: hydrogen bounded in bulk water (typical treatment) and hydrogen bounded in a lipid-like carbon chain molecule (polyethylene).

The results have shown that, in the case of thermal facilities (TRIGA and RA-3 reactors) with water phantoms, the simulations are in good agreement with measurements, but with phantoms of fatty tissue there were differences between measurements and calculations. These differences were lower for the simulation with the thermal scattering cross section for hydrogen in polyethylene. In the case of the epithermal facility (RA-6 reactor), the impact of the thermal library for hydrogen was not discernible.

These experiments in BNCT facilities, have shown the importance of using the appropriate thermal scattering treatment for each organic tissues in neutron transport for dosimetry calculations.

Comparative study of boron uptake by different tissues, with main focus on calcified tissues, administered as boric acid and boronophenylalanine in high doses

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Different boron compounds have been studied for application in BNCT (Boron Neutron Capture Therapy), in the treatment of different types of tumors, where the uptake of ^{10}B by tumoral tissue is of vital importance. Boric acid (BA) was originally used in this therapy for treating brain tumors. In the knowledge of the beneficial association between B and bone, we have begun to study the biodistribution in the bone of the B administered as boric acid at different doses and administration times, in order to define an appropriate dose for application in BNCT, and to learn more about its location in the bone tissue, since there are few studies to date on this subject. Chou and coworkers have reported the results of biodistribution of BA and others boronated compounds, but administered in minor doses that used in this work.

Our study focuses especially on calcified tissues, in view of potential treatment for certain bone tumors, e.g. those which have sectors undergoing bone formation, such as osteoblastic sarcoma. Osteosarcoma is the most common type of bone cancer in children and adolescents, especially between 10 and 19 years old. The most widely used boronated compound in clinical therapy is a D-fructose / L-*p*-boronophenylalanine (BPA) complex, thence our interest in comparative study.

In previous studies, we found high concentrations of B in calcified tissues when animals were infused with a solution of boric acid (BA). The aim of this study was to analyze boron uptake in these tissues and other metabolically important tissues by administrating boron in comparative doses in the form of two different compounds: BA and BPA, in doses of 40 mg B/ BW of animal (Group 40 BA and Group 40 BPA respectively). In Group 200 BA, administered with 200 mg B/BW of animal, we found large quantities of boron in diaphysis and epiphysis of normal Wistar rats, in the order of 200 ppm. A bone tissue/liver (or kidney) ratio of about 2.5 and bone tissue/skin ratio of 2 - 3 were found for Groups 200 and 40 BA. For animals infused with BPA solution, Group 40 BPA had bone tissue/ liver and bone tissue/skin ratios equal to or lower than 1. The bone tissue/skin ratio for animals infused with BA is seven times greater than the bone tissue/skin ratio for BPA animals infused. This results were obtained 3 hs post i.p. infusion. On the other hand, the skin, kidney and muscle are the tissue with upper uptake of BPA at this time. The boric acid seem to have more affinity by mineral tissue than organic tissue (soft tissue) improving notably the ratio between bone and organs of interest such as the skin which is dose limiting. The data obtained are particularly important to both the therapeutic approach and the radiotoxic approach in BNCT treatment of bone tumors.

Evaporation in Tissue Sections used for Neutron Autoradiography in BNCT

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Boron microdistribution in tissue samples from BNCT protocols can be studied by Neutron Autoradiography using nuclear track detectors (NTD). Boron concentration values can also be assessed by this technique, by means of a calibration curve that relates nuclear track density in the detector and ^{10}B atoms content.

Histological sections studied with this technique are obtained from frozen tissues at a cryostatic microtome (cryosectioning). Other methodologies used in BNCT to measure boron concentration, as alpha spectrometry, also use tissue samples obtained in this way. At the moment the tissue section is placed on the NTD after the cutting procedure, a process of evaporation and drying of the sample starts to come to room temperature. This fact causes a diminution in the sample mass, and a variation of the tissue slice thickness from the nominal value set at the cryostatic microtome, to the actual dimensions of the sample at the moment of irradiation with thermal neutrons. This phenomenon produces an increase in the concentration of ^{10}B atoms in the sample to be irradiated, and consequently an amplification of the number of nuclear tracks finally present in the detector. In order to quantify boron concentration of the original tissue sample, it is necessary to apply a correction factor or Evaporation Coefficient (CEv) that takes into account this effect.

In this work, evaporation mechanisms in this type of samples were outlined, as well as the various factors that may affect the process of mass variation and the final value of the coefficient. A protocol was designed to study the dynamics of evaporation in histological sections in our laboratory, in order to obtain Evaporation Coefficients for those tissues to be used in the boron quantification of biological samples from BNCT protocols. A software to collect and process measurements of mass variation of the tissue section as a function of time was developed, and environmental conditions such as pressure, temperature and humidity were simultaneously recorded. The mass was measured with a semi micro analytical scale (Cubis, Sartorius™).

Reproducible curves of evaporation and CEv results were obtained for tissue samples coming from BDIX rats, NUDE mice and hamsters. These results were compared with measurements made by thermogravimetry. Geometric factors that could affect the CEv values and tissues of different characteristics were studied. Curves of mass variation were evaluated with various models (mostly of the exponential type) found in the literature, and the best fit of the experimental points was determined.

The new methodology proved to be suitable for determining the CEv of histological sections. In heterogeneous tissues such as tumor and premalignant tissue, the feasibility of assessing the CEv is crucial, and the method here proposed can be applied to each tissue slice in particular using the equipment available in the laboratory. These studies will contribute to a more precise assessment of boron concentration in tissue samples, determined through the Neutron Autoradiography technique.

Gadolinium effect estimation of GAGG for BNCT-SPECT

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In boron neutron capture therapy (BNCT), there are some problems which must be solved in order to spead it widely. One of them is that the treatment effect (local dose) cannot be known during irradiation in real time. We thus have been developing a SPECT system for BNCT so- called BNCT-SPECT which can obtain a three-dimensional image of the treatment effect in real time. The principle is simple, i.e., to measure 478 keV gamma-rays promptly emitted from an excited state of the ^{7}Li nucleus generated by the ^{10}B(n,α) ^{7}Li reaction. However, it is difficult to selectively and accurately measure 478 keV gamma-rays, because capture gamma-rays of 2.22 MeV produced by ^{1}H(n, ɤ)^{2}H reaction and 511 keV annihilation gamma-rays become a critical background. For that purpose, a CdTe detector was selected as an elemental measuring device, because it has a high detection efficiency and excellent energy resolution. So far we examined theoretically and experimentally for the BNCT-SPECT system with the CdTe detector since about 10 years ago by the authors' group. In our previous research, we confirmed that the CdTe detector had enough performance as the elemental measuring device for the BNCT-SPECT system. On the other hand, a long operation for the measurement was seriously difficult due to polarization of the detector.

In present study, we have thus started to examine scintillators again, because recently very high performance scintillators were developed. In this study, we selected a GAGG scintillator which was expected to be feasible to realize the BNCT-SPECT system, since the GAGG scintillator has a high detection efficiency because of its high density and high light output yield. In addition, the energy resolution is good enough as an elemental measuring device for the BNCT-SPECT system. However, the GAGG scintillator contains gadolinium. Seemingly we cannot ignore the contribution from Gd capture gamma-rays in the GAGG scintillator because the neutron capture cross-section of Gd is remarkably large in the epithermal energy region. Therefore, we estimated numerically the contribution with MCNP-5 and investigated feasibility of the BNCT-SPECT using the GAGG scintillator.

As a result of investigation, we confirmed that the GAGG scintillator possessed sufficient performance to realize the BNCT-SPECT as the elemental measuring device. In addition, the contribution gamma-rays from Gd(n,ɤ) reaction was extremely small. Thereafter, we fixed the optimum dimensions of the GAGG scintillator to meet the requirements to realize the BNCT- SPECT system. In the next step, we will examine the designed GAGG scintillator experimentally to confirm whether it really possesses performance to realize the BNCT-SPECT system.

Feasibility study for estimation of hydrogen density distribution using MR imaging for pleural mesothelioma BNCT

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Four-port irradiation is generally applied to pleural mesothelioma BNCT in Kyoto University Research Reactor Institute (KURRI). The target dose is set to 7 Gy-eq in average for diseased lung. In the dose planning simulation, the whole of diseased lung is assumed to homogeneous and uniform, and the composition and density are fixed. Whereas the density of healthy lung is set to 0.1 g/mL, the density of diseased lung is set to 0.4 g/mL, four times larger, on the assumption of the retention of pleural effusion. In fact, the lung composition is heterogeneous. Particularly, the heterogeneity of hydrogen density influences thermal neutron distribution and it is resulted that the dose distribution is greatly influenced in BNCT. Then, we think that it is necessary to estimate the heterogeneity of the lung composition using diagnostic imaging and to utilize the estimated result in dose planning simulation. As one of the estimation methods for the lung heterogeneity, we are studying about the estimation of hydrogen density distribution using MR imaging. A feasibility study about this method is reported.

At first, the influence of the difference in hydrogen density of lung to dose planning was evaluated using SERA, in reference to a case of mesothelioma BNCT performed in KURRI. Here, the whole of lung was assumed to homogeneous composition, and the density was changed from 0.1 to 1.0 g/mL in 0.1 g/mL increment. Next, the possibility of the estimation of hydrogen density distribution using MRI was studied. Here, water in which the hydrogen density was regulated by mixing light water and heavy water, and oil were prepared as the measured samples.

From the SERA simulation, it was confirmed that the average thermal neutron flux for the diseased lung became maximum at the density of 0.2g/mL, and it decreased monotonously as the density increased. Based on the value at 0.1 g/mL, the flux decreased to 98%, 88% and 77% at 0.4 g/mL, 0.7 g/mL and 1.0 g/mL, respectively. For the total dose, it decreased to 100%, 94% and 85% for the similar densities. On the normalization to 7 Gy-eq for the mean dose of lung, the tumor dose for 0.4 g/mL decreased to 85% in mean dose and 89% in minimum dose, compared with the values for 0.1 g/mL. From the MRI experiment, it was confirmed that the hydrogen density distribution could be estimated within the error of 6%, when the proton density weighted image was selected as an MRI sequence. It was also confirmed that the estimation was possible using the other sequences, which were usually used in diagnosis.

We have a plan to make heterogeneous phantoms for lung composition, and to perform experiments using these phantoms for MRI imaging and neutron irradiation, in order to confirm the effectiveness of this method.

Development of neutron collimator for the new wide dynamic range neutron spectrometer for BNCT

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In BNCT, cases have been reported only using nuclear reactors as a neutron source. Recently, instead of nuclear reactors, accelerator-based neutron sources (ABNS) are being developed for BNCT. However, because of several limitations on ABNS, the neutron field of ABNS generally has a complex neutron spectrum. Therefore, it is very important to measure the neutron spectrum in the treatment area to determine the patient dose correctly. To resolve this issue, we have been developing a new neutron spectrometer for a wide dynamic energy range, from thermal to fast neutron regions, especially for epithermal neutron mainly used in BNCT. Our developing spectrometer works like the Bonner sphere spectrometer. It could measure the neutron spectrum with very high energy resolution by using a liquid material as a moderator to change its thickness finely. However, there is a very large problem for the development of our spectrometer; i.e., it is very difficult to validate the detector response function experimentally. Currently, we evaluate the detector response by Monte Carlo calculation using MCNP-5, with a specified calculation model. The calculated response function should thus be verified experimentally in the next step. So it is necessary to prepare a beam neutron source for the verification test for response function. However, it is known to be very difficult to design and construct it. In this study, we designed and developed a neutron collimator for that purpose, so as to reduce neutrons that are not incident on the desired region (sensor region) and at the same time so as not to change the neutron spectrum that are incident on the sensor region. Also we designed two kinds of neutron fields, one of which mainly includes thermal neutrons and the other was occupied by fast neutrons. With these two neutron fields the whole energy range could be covered for the experimental validation of our spectrometer. After the design, we constructed our neutron collimator which could be expected to collimate thermal and fast neutrons well, simultaneously suppressing distortion of the neutron spectrum by scattered neutrons from the surrounding materials. After that, the developed collimator's performance was confirmed by using imaging plates (IPs), IP-TR, sensitive for both gamma-rays and charged particles. An IP-TR was put on the exit of the collimator together with a radiator, e.g., a polyethylene, boron-composed polyethylene and so on, to change the IP's sensitivity for various neutron energies. Finally, we measured the neutron spatial distribution with the IP, and confirmed that this collimator could collimate the neutron field well. In future, we are going to validate the present neutron spectrometer with the neutron field with the developed collimator.

Investigation of beam component monitor for BNCT using gel detector.

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Objective

The measurement of the spatial distributions of the beam components is a way of the quality assurance and quality control for boron neutron capture therapy (BNCT). This study investigates the usage of the gel detector for this purpose. The investigation of the constituents of the gel to separate the beam components, i.e., thermal, epithermal and fast neutrons, and gamma rays is reported here.

Methods

The energy deposition to the gel was calculated using Monte Carlo calculations with PHITS. The assumed irradiation field was that by the standard epithermal neutron irradiation mode of Heavy Water Neutron Irradiation Facility of Kyoto University Research Reactor Institute. The gel assumed was a standard MAGAT type. The concentration of LiF doped to the gel was varied to change the influence by low energy neutrons. Here, the atomic composition of Li was 95 % for ^{6}Li. The beam of 10X10 cm^2 was assumed to be impinged on the gel cylinder of 20 cm in diameter and 20 cm in length. The concentration of ^{6}Li suitable to separate the beam components was investigated.

The investigations were performed for two types of usages, i.e., to monitor the 2-D distribution of the beam component on the gel surface and 3-D distribution inside the gel. For the former, the contribution of the beam component which entered the gel to the total energy deposition to the gel was calculated. For the latter, the contribution of the particle from which the energy deposition is derived, to the total energy deposition was calculated. Here, the energy deposition via electrons was regarded as a representative of gamma ray component, that via protons as the fast neutron component, and that via alpha particles and tritons as the thermal neutron component.

Result

For the usage to monitor along the gel surface, the contribution to the total energy deposition in the gel without ^{6}Li was 10-30 % for fast neutrons, 80-85 % for epithermal neutrons at depths over 4 cm, below 3 % for the others. For ^{6}Li concentrations at 1-10 wt%, fast neutron contribution was 60-85 % at depths over several centimeter from the upstream surface of the gel, which would be detectable. However, the gamma ray component was about 10 % and measurement test would be required to assure that it could be detected. For 100 ppm of ^{6}Li, the epithermal neutron contribution was over 90 %. This suggests the epithermal and fast neutron components are possibly measured by using the gel with ^{6}Li at 100 ppm to 10 wt %.

For monitoring the beam component distribution inside the gel, the contribution was 65-80 % for electrions, 10-30 % for protons, and 3-5 % for alpha particles and tritons, for 1 ppm of ^{6}Li. For higher ^{6}Li concentration, the contribution of alpha and tritons increased due to increase in $^{6}Li(n,\alpha)^{3}H$ reaction rate. At 100 ppm of ^{6}Li, the corresponding contributions were 14-32 %, 3- 9 %, and 68-82 %, respectively. However, in this case, the distribution inside the gel differed by 20 % for thermal neutron component, and several percent for the other components. In this cases, it was suggested the epithermal and fast neutron components, and gamma ray component could potentially be evaluated by combining the gels with ^{6}Li concentrations of 1, 10, and 100 ppm.

Study on irradiation field monitor for BNCT using multi imaging plate system.

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For the quality assurance and quality control for boron neutron capture therapy (BNCT), measuring the spatial distributions of neutrons and gamma rays is one of the potential and essential options. It is desirable to measure the beam components such as thermal, epithermal, fast neutrons and gamma rays, separately. This study designs and tests the multi imaging plate (IP) system for this purpose. The multi IP system consists of converters to enhance the components, and IPs. The principle of the system is as follows: thermal and epithermal neutrons will be enhanced with the secondary particles of the $^{10}B(n,\square)^{7}Li$ reaction in an epoxy resin doped with boron, fast neutrons with the recoiled protons from an epoxy resin. Then the enhanced components will be detected with the IPs. For gamma rays, the IP is originally sensitive, but the IP will be covered with carbon to shield that visible light that anneals the IP signal, without enhancing the neutron components. At first, the desirable configuration of the converters was surveyed using Monte Carlo calculations with PHITS. Then, a set of chosen converters was fabricated and tested experimentally. The validity of the fabricated system will be presented.

In calculation survey, the epoxy resin with about 1-10 wt% of ^{10}B of 1-5 mm in thickness was found to be options for thermal and epithermal neutrons. Carbon up to about 10 mm in thickness was suitable for gamma rays. However, fast neutrons were found difficult to enhance in BNCT fields. For the experimental test, the combination of the converters chosen as an potential option and fabricated was epoxy with B_4C at 6.85 wt% of 1 mm in thickness for thermal neutrons, that of 4 mm in thickness for epithermal neutrons, and 5 mm thick carbon for gamma rays. The irradiation was performed with the standard epithermal neutron irradiation mode of Heavy Water Neutron Irradiation Facility of Kyoto University Research Reactor Institute. The IP used was BAS-TR by Fuji Film Corporation, Japan.

As a result, plausible fluence distributions of epithermal neutrons and gamma rays were obtained, which suggests the validity of the multi imaging plate system. However, the obtained fluence of the thermal neutron component did not show the reasonable value. Optimizing the converters according to the field will improve the performance.

Proton beam of 5 mA in the Tandem Accelerator with Vacuum Insulation

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A source of epithermal neutrons based on a tandem accelerator with vacuum insulation for boron neutron capture therapy of malignant tumors was proposed and constructed in BINP. Stationary proton beam with 2 MeV energy, 1.6 mA current, 0.1% energy monochromaticity and 0.5% current stability was obtained in 2014. To increase the proton beam current the accelerator was upgraded in 2016. The modernization significantly suppressed the unwanted charged particle flows in the accelerator which resulted in the improved high voltage stability of acceleration gaps and enabled an increase in the proton beam current from 1.6 mA to 5 mA. What is the current value sufficient for BNCT? The report presents and discusses the details of the modernization, and the experimental results including the results of experiments on the long-term generation of neutrons at high current.

Beam Shaping Assembly for BINP Neutron Source

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Beam Shaping Assembly consisting of moderator, reflector and absorber, is used in accelerator neutron sources for forming of therapeutic neutron beam for Boron Neutron Capture Therapy. For the first time it is proposed to use BSA composite moderator: magnesium fluoride near neutron generating target and aluminum fluoride near the outlet, to use a composite reflector graphite in the front hemisphere and lead in the rear hemisphere, and to generate neutrons in the reaction ^{7}Li(p,n)^{7}Be with energy 2.3 MeV proton beam, rather than 2.5 - 2.8 MeV, usually considered. The method of numerical modeling of neutron transport and γ-radiation shows that the proposed solutions allow generating a therapeutic beam of neutrons that meets the requirements of BNCT to the greatest extent. The report presents and discusses BSA design manufactured for BINP epithermal neutron source based on vacuum insulation tandem accelerator.

Lithium Neutron Producing Target

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A source of epithermal neutrons for BNCT based on a tandem accelerator with vacuum insulation and lithium neutron producing target were proposed and constructed in BINP. The target is a thin layer of lithium deposited on a thin substrate intensively cooled. Prolonged exposure of the target protons 2 MeV led to the emergence of blisters on a copper substrate that is used at present. Proton fluence leading to blistering was determined. The comparison is given of the experimental value with the evaluative one obtained earlier at the experiments with the 100 and 200 keV proton beam. The results of the activation of the target and the beam transport channel with beryllium, and assumptions are made about the processes at target blistering. To increase the operation time of the target a tantalum substrate is proposed to be used. The new design of a target made with tantalum substrate implementing a number of new ideas is presented and discussed.

The Effect of Non-uniform Boron Distribution on Treatment Planning Dose Calculation

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Introduction

National Tsing Hua University and Taipei Veterans General Hospital started a clinical trial of boron neutron capture therapy (BNCT) for recurrent head-and-neck cancer at Tsing Hua open-pool reactor on August 11, 2010. Up to January 2016, 22 patients were treated. For each treatment, one week before the irradiation, patient's averaged tumor-to-normal tissue ratio (T/N ratio) of boron concentration was obtained from PET image after injection of ^{18}F-BPA. However, it has been observed that the boron distribution in tumor region was not uniform, and sometimes far from uniform. Hence a new feature of handling distributed boron PET information for more accurate treatment planning dose calculation was developed and added to the treatment planning system THORplan.

Materials and Methods

This new capability was applied to two cases selected from previous treatments, one for code verification purpose, and the other for investigating the degree of discrepancy due to non-uniform boron distribution. The 1st case chosen is one with small GTV volume and relatively uniform boron distribution. The 2nd case chosen is one with apparently non-uniformly distributed boron easily seen from the PET image. The contour of GTV was based on MRI image as usual.

Results

In the 1st case, the averaged T/N ratio was 2.71, while the distributed boron T/N ratio ranged from 1.87 to 3.49. The dose result of using distributed boron in treatment planning was quite close to the result of using uniform (average) boron distribution. In the 2nd case, the average T/N ratio was 4.56 while the distributed boron T/N ratio varied from 0.4 to 7.64. Under the same irradiation condition, the mean dose and the minimum GTV dose were very much overestimated when uniform average boron concentration was used for the whole GTV. Even if the GTV were divided into two regions, each with its own average T/N ratio 4.58 and 1.74, the mean dose and the minimum GTV dose were still overestimated by a factor of 1.07 and 2.3 respectively compared with the distributed boron results.

Conclusion

This new capability of incorporating PET information of distributed boron provides a more accurate way of dose evaluation during treatment planning, which will be helpful for establishing the correlation between clinical outcome and the dose delivered to the patient.

Thermal-hydraulic Design and Analysis of A New Cone Lithium Target for BNCT

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Abstract

One of the challenging issue of Boron Neutron Capture Therapy (BNCT) solid lithium target is cooling for the low melting point of lithium and high heat flux. An new designed cone base structure made of copper with optimized cooling structure is shown here. The cone roof has a sphere surface, is cooled by jet cooling with a suitable size and velocity, and the rest zone of this cone is cooled by straight mini-channels connected with the jet flow. Also, thermal simulation for 30 kW is carried out with Computational Fluid Dynamics (CFD) associated with shear-stress transport k-omega turbulent model, and the temperature and velocity distribution are given in this paper. Results show that the maximum temperature is 363 K for the highest flux in the roof jet stagnation zone. For the heat transfer area in the mini-channel zone is constant, the temperature is raised sharply from roof to bottom for the heat flux is constant but the diameter is increased. There is no backflow after the flow past the sphere surface in this design, and meet the high efficient cooling demand. From the temperature distribution, the new cone target is possible for 30 kW and even higher.

Thermal Neutron Fluence and Gamma-ray Dose QA Using CaF_2:Mn TLD for BNCT Beam at THOR

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Four dose components, namely, gamma-ray dose, fast and epithermal neutron dose, nitrogen dose, and boron dose are produced when the BNCT beam enters the treated patient. The physical quantities of interest of these dose components are tissue gamma-ray dose, tissue fast and epithermal neutron dose, and thermal neutron fluence, since nitrogen dose and boron dose are determined primarily by thermal neutron fluence. In the PMMA QA phantom with dimensions of 21 x 21 x 21 cm^3 exposed to the BNCT beam at THOR (Tsing Hua Open-pool Reactor), the tissue fast and epithermal neutron dose is much smaller than the tissue gamma- ray dose. Therefore, thermal neutron fluence and tissue gamma-ray dose are deemed the most interested physical quantities for QA measurements. CaF_2:Mn TLDs contain an adequate amount of Mn with a weight percent of around 1.6% for neutron activation and are essentially insensitive to neutrons with dose components of less than 3% in measurement locations in the QA phantom. Accordingly, a QA process for thermal neutron fluence and gamma-ray dose measurement simultaneously in the phantom by sing CaF_2:Mn TLDs was established for the BNCT beam at THOR. In this QA process, each CaF_2:Mn TLD chip (TLD-400) with dimensions of 3.2 x 3.2 x 0.89 mm^3 was treated as an individual detector with its own ID. A sophisticated annealing and readout process for TLD-400 has been established. By using this procedure the reproducibility of each TLD-400 chip can be good within 1% for an exposure of 500 mGy. It was found that CaF_2:Mn TLD can emit prominent scintillation lights and after the calibration using the direct comparator method of Neutron Activation Analysis, these scintillation lights were taken advantage of using the TLD reader without heating to measure the activity of Mn-56 induced in the TLD chip. The TL signal of the irradiated CaF_2:Mn chip represented essentially the TLD gamma-ray dose with a tiny neutron component of less than 3%. A small TL contribution caused by the decay of Mn-56 and a little contamination of scintillation lights during TL readout have also been corrected. Finally, the TLD gamma-ray dose was converted to the tissue gamma-ray dose by a conversion factor of around 1.1.

Experimental Estimation of Neutron Yield from ^{7}Li(p,n) Reaction for Source Term Estimation System for BNCT

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Our research group has been developing an accelerator-based neutron source(ABNS) for BNCT. The ABNS project of Osaka University employs an electrostatic accelerator which produces low energy neutrons via p-Li (^{7}Li(p,n)^{7}Be) reaction. This neutron yield and angular distribution are known to be affected by the ^{7}Li enrichment, chemical form, and thickness of target. Therefore, it is important for an optimum ABNS design to compare and examine characteristics of various kinds of targets. However, very few systems estimating their neutron yields and angular distributions were proposed. The present study aims at development of an easy-to-use calculation code system to evaluate the source term performance of accelerator based neutron sources. In the present study, experimental results necessary for validation of the system are described in parallel with development of the system.

At first, we made three kinds of targets composed of thick ^{nat}Li metal plate, ^{7}Li-enriched one and LiF plate. The targets were bombarded with 2.5, 2.7, 2.9 MeV protons using the Dynamitron accelerator at Fast Neutron Laboratory in Tohoku University. To determine the neutron yield accurately, we measured two objects. One is the number of incident protons and the other is the number of generated neutrons. The number of protons incident on the Li target was measured directly from the target current with a current integrator. As for the number of neutrons generated, since it is exactly the same number of ^{7}Be, we measured 478keV gamma-rays emitted via ^{7}Be decay to^{7}Li in the half-life of 53 day with a handy CdTe detector before and after the irradiation and successfully determined the exact number of neutrons.

From the measurement results, we found that the neutron yield of ^{nat}Li was twice larger than that of LiF, and the ratio of the values (^{nat}Li/LiF) showed different depending on the incident proton energy. Furthermore other results (Lee et al. and Yanch et al.) supported the presently measured values.

Completing development of the present system, we are validating it and will expand the system to be able to estimate performance of various neutron source terms for various targets and energies.

Investigation of Methods of Establishing Equivalent Surface Source for BNCT Treatment Planning Calculation

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Introduction

Accelerator-based BNCT has become more and more attractive since its facility can be installed in the hospital. For clinical purpose, an equivalent surface source at the neutron beam exit is needed for reducing computing time of treatment planning dose calculation. Two approaches of generating surface source at the neutron beam exit were investigated in this study.

Materials and Methods

Method 1 is to tally the energy, angular and radial distributions of neutrons at beam exit by using F1 tally in the Monte Carlo calculation to establish a primary source at the beam port and secondary sources representing leaking neutrons outside the beam port radius. The radius of the primary source is 7 cm. The radii of secondary sources are from 7 to 9 cm and from 9 to 11 cm respectively. Since MCNPX only allows one level of dependence of source variable and the coupled energy-angle distribution in a given region does not seem to vary much with the radius, the radial dependence of source is separated. Method 2 is to establish the source by using surface source write SSW function of MCNPX which recorded the position, energy and direction of every neutron crossing the specific surface. The history cutoff used is 4×10^8.

Results

The accuracies of these two sources were evaluated by comparing the fluxes of in-phantom calculation with reference calculation. The reference in-phantom result was calculated directly from neutron source generated by ^{9}Be(p,n)B reaction and passing through beam shaping assembly. Weight window technique was used to reduce the statistical errors. Comparing the results calculated by using neutron sources established by Method 1 with the reference case, for phantom located 10 cm away from the collimator exit, the total neutron flux along the centerline of the phantom was about 10% higher. On the other hand, the performance of the source generated by Method 2 was quite satisfactory. Comparing to the reference result, the differences of thermal and epithermal neutron fluxes in the phantom were < 1 %. The difference in fast neutron flux was ~ 2.4%, close to the statistical uncertainties of individual calculations.

Conclusion

There are many approximations needed to be made in Method 1 to establish a surface source, including the proper choice of dependency of variables. However, the discrepancy of in-phantom result was believed to be mainly due to the limitation of describing the azimuthal angle dependence of the surface source in the subsequent Monte Carlo dose calculation. Method 2 using SSW is a better choice for generating equivalent surface source for treatment planning system using MCNP as the dose calculation kernel.

The Boron Neutron Capture Therapy (BNCT) Program at the University of Missouri, International Institute of Nano and Molecular Medicine (I²NM²)

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Boron neutron capture therapy (BNCT) is a cancer cell-selective, targeted binary radiation treatment method based upon the facile capture of a slow neutron by a boron-10 nucleus. The capture reaction produces a high energy □-particle ($^4He^{2+}$), a lithium ion ($^7Li^{3+}$) and a gamma photon along with ~2.4 MeV of kinetic energy. The short trajectory (5-9 μm or one cell diameter) of these ions enables the selective destruction of cancer cells without damaging neighboring healthy cells. One of the important requirements for a successful BNCT therapy is the capability to selectively deliver sufficient concentration of boron-10 to the tumor tissue. The International Institute of Nano and Molecular Medicine (I²NM²) has developed a highly tumor selective boron-rich liposomal nanoparticle transport system that delivers therapeutic dose of boron-10 to the tumor tissue. The liposomal nanoparticle takes advantage of tumor's leaky vasculature to deliver boron-10 through EPR effect (enhanced permeation and retention effect).

The boron-rich liposomal nanoparticle consists of phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol. The lipophilic *nido*-carborane, K[*nido*-7-$CH_3(CH_2)_{15}$-7,8-$C_2B_9H_{11}$] (MAC) is incorporated in the lipid bilayer membrane and the hydrophilic polyhedral borane, Na_3[1-(2'-$B_{10}H_9$)-2-$NH_3B_{10}H_8$] (TAC) is encapsulated in the aqueous core. These nanoscale (100-130 nm) therapeutic agents were effective in treating mice implanted with EMT6 (mammary tumor cell line) and CT26 (colon cancer cell line) tumor cells using the thermal neutron beam at the University of Missouri Research Reactor (MURR). Highly selective and localized boron accumulation (~60 ppm) in tumor was seen over a period of 30-48 hours. In comparison, there were low concentrations of boron in blood and surrounding healthy tissues. Reduction of tumor growth rate was seen in mouse patients without radiation damage and boron agent toxicity. An overview of the BNCT research at I²NM² will be presented.


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ICNCT-17
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