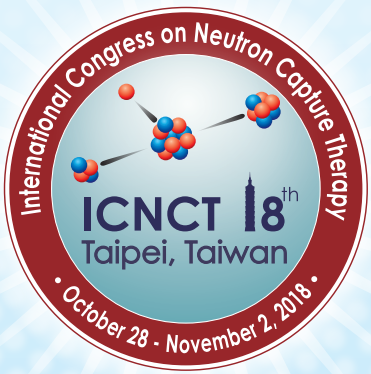
18th International Congress on Neutron Capture Therapy

October 28 - November 2, 2018 TAIPEI, TAIWAN



Abstract Book

Contents

Time/Date	Oct. 28 Sun	Oct. 29 Mon	Oct. 30 Tue	Oct. 31 Wed	Nov. 1 Thu	Nov. 2 Fri
08:00-08:30						
08:30-09:00						
09:00-09:30		08:50-09:20 **Opening Ceremony** (R1101)	09:00-10:40 **Invited Lecture(IL2)** Amanda E. Schwint Rolf Barth Silva Bortolussi Saverio Altieri Hanna Koivunoro (R1001)	09:00-10:40 **Invited Lecture (IL4)** Koji Ono Hiroaki Kumada Jun Hatazawa Sandro Rossi Shin-Ichi Miyatake (R1001)	09:00-10:30 **Plenary Lecture (PL)** R Shin-ichiro Masunaga Fong-In Chou Mitsuko Masutani Jeng-Jong Hwang P2 Ignacio Porras Sánchez Yuan-Hao Liu (R1001)	09:00-10:30 **Parallel Sessions (Pa)** P6 R1001 R3 R1002 B3 R1003
09:30-10:00		09:20-10:50 Hatanaka Award Lecture (R1101)				
10:00-10:30						
10:30-11:00		10:50-11:10 **Coffee Break**	10:40-11:00 **Coffee Break**	10:40-11:00 **Coffee Break**	10:30-10:50 **Coffee Break**	10:30-10:50 **Coffee Break**
11:00-11:30		11:10-12:30 **Invited Lecture (IL1)** Akira Matsumura Leena Kankaanranta Minoru Suzuki Hiroyuki Nakamura (R1101)	11:00-12:00 **Invited Lecture (IL3)** Tatsuhiko Sato Andres J. Kreiner Detlef Gabel (R1001)	11:00-12:00 **Plenary Lecture (PL)** Cl2 Hiroshi Fukuda Yuan-Hung Wu Ko-Han Lin Yi-Wei Chen (R1001)	10:50-12:20 **Plenary Lecture (5)** M Kazuyo Igawa Yung-Jen Chuang Ch Po-Shen Pan Ming-Hsin Li Jen-Kun Chen Mitsunori Kirihata (R1001)	10:50-11:30 **Closing Ceremony** (R1001)
11:30-12:00						11:30-12:30 **Executive Board Meeting & Board of Councilors Meeting** (R1006)
12:00-12:30			12:00-12:30 **Plenary Lecture (PL)** P1 Hiroki Tanaka Yoshinori Sakurai (R1001)			
12:30-13:00	12:30-13:30 **Executive Board Meeting** (R1006)	12:30-13:30 **Lunch** **Luncheon Seminar** (Stella Pharma) (R1001)	12:30-13:30 **Lunch** **Luncheon Seminar** (Neutron Therapeutics, Inc) (R1001)	12:30-18:00 **Technical Tour to THOR**	12:20-13:20 **Lunch**	12:30-18:00 **Optional Tour**
13:00-13:30						
13:30-14:00	13:30-15:00 **Board of Councilor's Meeting** (R1006)	13:30-14:30 **Plenary Lecture (PL)** Cl1 Yoshihiro Takai Shinji Kawabata Zi-zhu Zhang Ling-Wei Wang (R1001)	13:30-15:00 **Poster Viewing& Presentation** (R1010)		13:20-14:00 **Election Board Coun.**	
14:00-14:30					14:00-15:30 **Poster Viewing& Presentation** (R1010)	
14:30-15:00		14:40-15:40 **Parallel Sessions (Pa)** Cl2 R1001 B1 R1002 Ch1 R1003				
15:00-15:30	15:10-17:40 **Training Course (TC)** Rolf Barth Koji Ono Amanda E. Schwint Hiroaki Kumada (R1003)		15:00-16:00 **Parallel Sessions (Pa)** Ch2 R1001 R1 R1002 B2 R1003			
15:30-16:00		15:40-16:00 **Coffee Break**			15:30-15:50 **Coffee Break**	
16:00-16:30		16:00-18:00 **Parallel Sessions (Pa)** P1 R1001 P2 R1002 M1 R1003	16:00-16:20 **Coffee Break**		15:50-17:00 **Parallel Sessions (Pa)** P5 R1001 R2 R1002 Ch3 R1003	
16:30-17:00			16:20-18:00 **Parallel Sessions (Pa)** P3 R1001 Cl2 R1002 P4 R1003			
17:00-17:30					17:00-18:00 **General Assembly** (R1001)	
17:30-18:00						
18:00-18:30	18:00-20:00 **Welcome Reception** (B1)					
18:30-19:00				18:30-20:30 **Congress Banquet** (Howard Hotel B2)		
19:00-19:30						
19:30-20:00						
20:00-20:30						

TC : Training Course

IL : Invited Lecture

PL : Plenary Lecture

Pa: Parallel Sessions

PS: Poster Viewing & Presentation

Cl : Clinical matters

R : Radiation biology

Ch : Chemistry & Pharmacology

P : Physics & Engineering

B : Boron determination & Imaging technology

M : Miscellaneous

Time Table

SUN 10 / 28

Sunday, October 28, 2018

CHANG YUNG-FA FOUNDATION International Convention Center

12:30-13:30	**Executive Board Meeting**	R 1006
13:30-15:00	**Board of Councilors Meeting**	R 1006
15:10-17:40	Training Course (TC)	R 1003
15:10-15:40 **Invasion, Metastasis and Tumor Angiogenesis** **Rolf Barth**, Department of Pathology, Ohio State University, Columbus, Ohio, USA		
15:40-16:10 **Consideration on the effect of heterogeneous distribution of boron drug in tumor tissue on final tumor control by BNCT** **Koji Ono**, Osaka Medical College / Kansai BNCT Medical Center, Japan		
16:10-16:40	**Coffee Break**	
16:40-17:10 **Optimization of drug delivery and therapeutic effects based on the knowledge of BNCT radiobiology** **Amanda E. Schwint**, Department of Radiobiology, National Atomic Energy Commission, Argentina		
17:10-17:40 **PHYSICS / Neutron Source** **Hiroaki Kumada**, University of Tsukuba, Faculty of Medicine, Japan		

18:00-20:00	**Welcome Reception**	B1

MON 10 / 29

Monday, October 29, 2018

CHANG YUNG-FA FOUNDATION International Convention Center

08:50-09:20	**Opening Ceremony**	R 1101
09:20-10:50	Hatanaka Award Lecture Chairpersons: Akira Matsumura, Koji Ono	R 1101
09:20-09:50 **Developing study on low molecular boron compounds for BNCT, their design, synthesis, detection and biological evaluation** **Mitsunori Kirihata,** OPU Research Center for BNCT, Japan		
09:50-10:20 **Clinical Trials of BNCT for melanoma and H&N tumor in Japan — contribution of BPA —** **Junichi Hiratsuka**, Department of Radiation Oncology, Kawasaki Medical School, Japan		
10:20-10:50 **The privilege of working together for BNCT** **Amanda E. Schwint**, Department of Radiobiology, National Atomic Energy Commission, Argentina		

10:50-11:10	**Coffee Break**	

11:10-12:30	Invited Lecture (IL1) Chairpersons: Akira Matsumura, Koji Ono	R 1101
11:10-11:30 (IL1 01) **Current status of i-BNCT project at Tsukuba & Tokai** **Akira Matsumura**, Department of Neurosurgery, University of Tsukuba, Japan		
11:30-11:50 (IL1 02) **BNCT in Finland.** **Leena Kankaanranta**, HUCH, Helsinki University Central Hospital, Finland Comprehensive Cancer Center Departments of Oncology and Radiation Therapy, Finland		
11:50-12:10 (IL1 03) **Comparison of the BPA-BNCT for unresectable liver metastases at KUR and at Triga Mark II** **Minoru Suzuki**, Institute for Integrated Radiation and Nuclear Science, Kyoto University / Particle Radiation Oncology Research Center, Japan		
12:10-12:30 (IL1 04) **Albumin-Based Boron Delivery to Tumor** **Hiroyuki Nakamura**, Laboratory for Chemistry and Life Science (CLS), Institute of Innovative Research, Tokyo Institute of Technology, Japan		

12:30-13:30	Luncheon Seminar	R1001
Research and Development of Boron Drugs for BNCT by Industry-University Collaboration in Japan. **STELLA PHARMA**		

13:30-14:30	Plenary Lecture -Clinical matters 1 (PL Cl1) Chairpersons: Yoshihiro Takai, Shinji Kawabata	R1001
13:30-13:45 (PL Cl1 01) Accelerator-based BNCT at Southern TOHOKU general hospital--The world's first BNCT Hospital-Roadmap to Pharmaceutical Affairs Regulatory Approval **Yoshihiro Takai**, Southern TOHOKU BNCT research center, Japan		
13:45-14:00 (PL Cl1 02) Successful result in Overall Survival from Phase II Clinical Study of BNCT with XRT/TMZ in Patients with Newly Diagnosed Glioblastoma **Shinji Kawabata**, Osaka Medical College / Neurosurgery, Japan		
14:00-14:15 (PL Cl1 03) Biodistribution studies of boronophenylalanine-fructose complex in different types of skin melanoma **Zi-Zhu Zhang**, Beijing Nuclear Industry Hospital/Nuclear Medicine Department Beijing Capture Technology Limited Co./ Research and Development Department, China		
14:15-14:30 (PL Cl1 04) Boron neutron capture therapy (BNCT) combined with image-guided intensity modulated radiotherapy (IG-IMRT) for treatment of recurrent Head & Neck cancer **Ling-Wei Wang**, Taipei Veterans General Hospital/Department of oncology, Taiwan		

14:40-15:40	Parallel Session (Pa)	R1001, R1002, R1003
Clinical matters (Cl1) Chairpersons: Shin-Ichi Miyatake, Minoru Suzuki		R1001
14:40 (Pa Cl1 01) Salvage Boron Neutron Capture Therapy (BNCT), Treatment Experiences of Recurrent Malignant Brain Tumors in Taiwan **Tien-Li Lan**, Division of Radiotherapy, Department of Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan		
14:52 (Pa Cl1 02) Results of phase 1 clinical trial of accelerator-based BNCT for recurrent malignant gliomas **Shin-Ichi Miyatake**, Cancer Center, Osaka Medical College, Japan		

15:04 (Pa Cl1 03) BNCT for Head and Neck Cancer : Summary of reactor irradiation. **Teruhito Aihara**, Kansai BNCT Medical Center, Osaka Medical College, Takatsuki, Japan	
15:16 (Pa Cl1 04) Defining the molecular characteristics of boron compounds proposes the concept of precision medicine in BNCT field **Seiji Yasui**, Neutron Therapy Research Center, Okayama University, Japan	
15:28 (Pa Cl1 05) Comparison between SUVmax, TNR, and TBR in 18F-BPA PET. Which index is correlated best with 18FDG uptake? **Hiroshi Igaki**, Department of Radiation Oncolcogy, National Cancer Center Hospital, Tokyo, Japan	
Boron determination & Imaging technology (B1) Chairpersons: Agustina Portu, Alexander Winkler	R1002
14:40 (Pa B1 01) A virtual neutron anti-scatter grid for future Cd(Zn)Te based BNCT-SPECT systems **Alexander Winkler**, Helsinki Institute of Physics, University of Helsinki, Finland	
14:52 (Pa B1 02) Boron analysis and imaging of 2hr-BPA-exposured cells by using micro proton particle induced gamma-ray emission (PIGE). **Kei Nakai**, Ibraki prefectural University of Health Sciences, Ibaraki, Japan	
15:04 (Pa B1 03) Neutron autoradiography combined with UV-C sensitization: towards intracellular localization of boron **Agustina Portu**, National Atomic Energy Commission (CNEA), Argentina	
15:16 (Pa B1 04) Neutron autoradiography approaches to study microdistribution of boron compounds in a diffuse lung metastases experimental model **Agustina Portu**, National Atomic Energy Commission (CNEA), Argentina	
15:28 (Pa B1 05) Single Cell ICP-MS: Quantification of Metal Content in Individual Cells - An Insight into Cancer Treatment **Chady Stephan**, PerkinElmer Canada, Ontario, Canada	
Chemistry & Pharmacology (Ch1) Chairpersons: Hiroyuki Nakamura, Getlef Gabel	R1003
14:40 (Pa Ch1 01) Metabolism-controlled boron delivery systems composed of p-boronophenylalanine and poly(vinyl alcohol) **Takahiro Nomoto**, Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology, Yokohama, Japan	

14:52 (Pa Ch1 02)
Preclinical study on boron neutron capture therapy for bone metastasis with human breast cancer cell lines
Tooru Andoh, Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University, Kobe, Japan

15:04 (Pa Ch1 03)
Synthesis and radiolabelling (124I) of multifunctionalised gold nanorods (AuNRs) as boron drug delivery agents using a pretargeting strategy based on bioorthogonal 'click reaction' with application in Boron Neutron Capture Therapy.
Irene V. J. Feiner, Radiochemistry and Nuclear Imaging, CIC biomaGUNE, San Sebastian, Spain

15:16 (Pa Ch1 04)
Enhanced tumor-targeted delivery of p-boronophenylalanine using fructose-functionalized polymers for boron neutron capture therapy
Ying Yao, Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology, Yokohama, Japan

15:40-16:00	**Coffee Break**	**R1010**

16:00-18:00	Parallel Session (Pa)	R1001, R1002, R1003

Physics & Engineering (P1) — **R1001**
Chairpersons: Sergey Taskaev, Kiyotaka Akabori

16:00 (Pa P1 01)
Accelerator Neutron Source for in-vitro and in-vivo BNCT studies
Sergey Taskaev, Budker Institute of Nuclear Physics, Russia

16:12 (Pa P1 02)
In Situ Observations of Blistering of a Metal Irradiated with 2-MeV Protons
Sergey Taskaev, Budker Institute of Nuclear Physics, Russia

16:24 (Pa P1 03)
A real-time neutron monitor for BNCT
Kiyotaka Akabori, Sumitomo Heavy Industries, Ltd., Japan

16:36 (Pa P1 04)
Development of the accelerator based Boron Neutron Capture Therapy system for cancer treatment within 1-hour therapeutic time
D.S. Kim, Department of pulse and accelerator, Dawonsys, Gyeonggi-do, Korea

16:48 (Pa P1 05)
Development and experimental verification of a liquid moderator based neutron spectrometer
Shingo Tamaki, Graduate school of Engineering, Osaka University, Japan

17:00 (Pa P1 06)
Monte Carlo Simulation and Experimental Characterization of Tissue Equivalent Proportional Counter (TEPC) for Neutron Dosimetry
Justin Malimban, Program in Biomedical Radiation Sciences, Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

17:12 (Pa P1 07)
Study of the role of neutron induced nuclear reactions on chlorine in healthy tissue dosimetric calculations for BNCT. Measurement of their cross sections at n_TOF (CERN).
Francisco Ogallar, University of Granada, Spain

17:24 (Pa P1 08)
Evaluation of silicon based microdosimetry for boron neutron capture therapy Quality Assurance using fast neutron beams
James Vohradsky, Centre for Medical Radiation Physics, University of Wollongong, Australia

17:36 (Pa P1 09)
Uncertainties in the absorbed dose determination in irradiations with epithermal neutrons due to the dependence of neutron transport on shape and size of the exposed volume
Grazia Gambarini , Department of Physics, University of Milan, Milan, Italy

17:48 (Pa P1 10)
Commissioning of The Nubeam BNCT Neutron Source at Helsinki University Hospital Cancer Center
Liisa Porra, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

Physics & Engineering (P2) — **R1002**
Chairpersons: Hiroaki Kumada, Katarzyna Tyminska

16:00 (Pa P2 01)
Beam characteristics and in phantom dosimetry for accelerator-based boron neutron capture therapy: Comparative study of Monte Carlo simulations using Geant4 and MCNP6
Hyegang Chang, Program in Biomedical Radiation Sciences, Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

16:12 (Pa P2 02)
Development status of BNCT Treatment Planning System: SACRA planning
Tetsuya Mukawa, Sumitomo Heavy Industries Ltd., Japan

16:24 (Pa P2 03)
Neutron beam quality measurement of accelerator-based neutron source using microdosimetric technique
Naonori Hu, Graduate School of Engineering, Kyoto University, Kyoto, Japan

16:36 (Pa P2 04)
Characterization Study of Boron-10 Doped Nanodiamonds Made by Ion Implantation
Bo-Rong Lin, Institute of Electronics, National Chiao Tung University, Hsinchu, Taiwan

16:48 (Pa P2 05)
A New Boron Delivery Agent: Boron-10 Doped Nanodiamonds Made by Ion Implantation
Tzung-Yuang Chen, Health Physics Division, Nuclear Science and Technology Development Center, National Tsing Hua University, Hsinchu, Taiwan

17:00 (Pa P2 06)
BNCT Research Facility at Maria Reactor (NCBJ, Poland) – Numerical Models and First Measurements
Katarzyna Tyminska, National Centre for Nuclear Research, Otwock, Poland

17:12 (Pa P2 07)
Verification for dose estimation performance of a Monte-Carlo based treatment planning system in University of Tsukuba
Hiroaki Kumada, University of Tsukuba, Faculty of Medicine, Japan

17:24 (Pa P2 08)
Development of a novel patient setting & real-time monitoring system using motion capture technology for boron neutron capture therapy
Hiroaki Kumada, University of Tsukuba, Faculty of Medicine, Japan

17:36 (Pa P2 09)
Effect of fast neutron and gamma-ray ratios on a dose distribution in a water phantom
Yoshiaki Kiyanagi, Research Laboratory of Accelerator-based BNCT system, Graduate School of Engineering, Nagoya University, Nagoya, Japan

17:48 (Pa P2 10)
Radiation quality dependence of polymer gel dosimeters in therapeutic neutron irradiation field
Ryohei Uchida, Graduate School of Engineering, Kyoto University, Kyoto, Japan

Miscellaneous (M1) **R1003**
Chairpersons: Ching-Shen Liu, Hironobu Yanagie

16:00 (Pa M1 01)
A practical handling of the limitation of absorbed dose in BNCT
Tooru Kobayashi, K2BNCT Science & Engineering Laboratory Co. Ltd, Japan

16:12 (Pa M1 02)
Development of Proton Linear Accelerator based Boron Neutron Capture Therapy System in Republic of Korea
Hyo Jung Seo, Department of R & D, Dawonmedax, Seoul, Korea

16:24 (Pa M1 03)
Cherenkov radiation and its application in Boron Neutron Capture Therapy
Diyun Shu, Department of Nuclear Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing, China

Daily Program

MON 10 / 29

16:36 (Pa M1 04)
Strategies for consistently assessing the response of radiochromic film using flatbed scanners
Xudong Zhang, Department of Nuclear Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing, China

16:48 (Pa M1 05)
Current Status of BNCT Clinical Trials in Japan
SHIN Masui, Sumitomo Heavy Industries, Ltd., Industrial Equipment Division, Tokyo, Japan

17:00 (Pa M1 06)
Preparation of Water-in-Oil-in-Water Emulsion as Drug Delivery System Using Mixing Medical Device for Neutron Capture Therapy
Hironobu Yanagie, Research Institute of Healthy Living, Niigata University of Pharmacy & Applied Life Sciences, Niigata, Japan

17:12 (Pa M1 07)
Development of remote-changeable Bonner sphere spectrometer
Sadaaki Shirashi, Graduate School of Engineering, Kyoto University, Kyoto, Japan

17:36 (Pa M1 08)
Reactor Laboratory for Biomedical Research in The National Centre for Nuclear Research, Poland
Edyta Michas, National Centre for Nuclear Research, Poland

17:48 (Pa M1 09)
The overview and prospects of BNCT facility at Tsing Hua Open-pool Reactor
Shiang-Huei Jiang, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan

Tuesday, October 30, 2018

CHANG YUNG-FA FOUNDATION International Convention Center

09:00-10:40	**Invited Lecture (IL2)** Chairpersons: Rolf Barth, Amanda E. Schwint	R 1001

09:00-09:20 (IL2 01)

Translational Radiobiological BNCT Studies for the Treatment of Head and Neck Cancer, Liver and Lung Metastases, Rheumatoid Arthritis and Induction of Abscopal Effect: A Bench to Bedside Approach

Amanda E. Schwint, Department of Radiobiology, National Atomic Energy Commission, Argentina

09:20-09:40 (IL2 02)

A realistic appraisal of boron neutron capture therapy as a cancer treatment modality

Rolf Barth, Department of Pathology, Ohio State University, Columbus, Ohio, USA

09:40-10:00 (IL2 03)

Dosimetry assessment in patients using a neutron beam based on RFQ accelerator for future installation in a hadrontherapy centre.

Silva Bortolussi, Department of Physics, University of Pavia and INFN, Unit of Pavia, Italy

10:00-10:20 (IL2 04)

Neutron induced charged particles spectrometry for Boron concentration measurement

Saverio Altieri, Physics Department, Pavia University, Italy

10:20-10:40 (IL2 05)

A Retrospective Analysis of Dose Responses after Boron Neutron Capture Therapy for Locally Recurrent Head and Neck Squamous Cell Carcinoma

Hanna Koivunoro, Neutron Therapeutics Inc., Finland

10:40-11:00	**Coffee Break**	R 1010

11:00-12:00	**Invited Lecture (IL3)** Chairpersons: Hiroki Tanaka, Tatsuhiko Sato	R 1001

11:00-11:20 (IL3 01)

Macro- and microdosimetry for BNCT based on PHITS

Tatsuhiko Sato, Japan Atomic Energy Agency, Nuclear Science and Engineering Center, Japan

11:20-11:40 (IL3 02)

Status of Accelerator-Based BNCT worldwide and in Argentina

Andres J. Kreiner, CNEA. National Atomic Energy Commission of Argentina

11:40-12:00 (IL3 03)

Carbon or Boron: Does it matter in BNCT drugs?

Detlef Gabel, Jacobs University Bremen/ Life Sciences and Health, Germany

12:00-12:30	**Plenary Lecture - Physics & Engineering (PL P1)** Chairpersons: Hiroki Tanaka, Tatsuhiko Sato	R1001

12:00-12:15 (PL P1 01)

Development of thermal neutron irradiation port for cells and small animals using 20MeV cyclotron and beryllium target

Hiroki Tanaka, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

12:15-12:30 (PL P1 02)

The history of the development of reactor-based neutron source for BNCT

Yoshinori Sakurai, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

12:30-13:30	**Luncheon Seminar**	R1001

Neutron Therapeutics Lunch Symposium

Neutron Therapeutics, Inc.

13:30-15:00	**Poster Viewing & Presentation 1 (PS1)**	R1010

Poster Group I (Clinical matters / Boron determination & Imaging technology)

13:30 (PS1 Cl 01)

Reirradiation of Locally Recurrent Head and Neck Cancer with BNCT or Proton Therapy: a Systematic Review

Chi-Shuo Lin, Taipei Veterans General Hospital, Taiwan

13:36 (PS1 Cl 02)

Recycling 10B-enriched Boronophenylalanine in Urine of Patients with Recurrent Brain Tumor

Nai-Chun Huang, Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes, Miaoli, Taiwan

13:42 (PS1 Cl 03)

Boron neutron capture therapy in 45 patients with recurrent head and neck cancers who have no other treatment options.

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

13:48 (PS1 Cl 04)

Evaluation of the impact on a change of patient's posture from preplan with diagnostic images to treatment position in boron neutron capture therapy

Tomoaki Motoyanagi, Southern Tohoku BNCT Research Center, Koriyama, Japan

13:54 (PS1 B 01)
Design of collimator for T/N-SPECT for BNCT
Saki Shibata, Division of Sustainable Energy and Environmental Engineering, Graduate School of Engineering Osaka University, Japan

14:00 (PS1 B 02)
The specific retention of boric acid in liver tumor for BNCT in a single liver tumor-bearing rat and a multifocal liver tumor-bearing rabbit models
F. I. Chou, Nuclear Science and Technology Development Center, National Tsing Hua University, Hsinchu, Taiwan

14:06 (PS1 B 03)
Simulations of an imaging system based on a CZT photon detector for a future BNCT-SPECT.
Setareh Fatemi, National Institute of Nuclear Physics INFN, Unit of Pavia, Pavia, Italy

14:12 (PS1 B 04)
Preliminary performance studies of a CZT photon detector using a highly thermalized neutron beam.
Nicoletta Protti, National Centre for Nuclear Research, Italy

14:18 (PS1 B 05)
High performance 3D CZT spectro-imager for BNCT-SPECT: preliminary characterization.
Nicoletta Protti, National Centre for Nuclear Research, Italy

14:24 (PS1 P 01)
Feasibility study of using IRT-T research reactor for BNCT applications
Mikhail Anikin, National Research Tomsk Polytechnic University, Russia

14:30 (PS1 P 02)
Data processing automatization and improvements of D-Pace OWS-30 wire scanner
Timofey Bykov, Budker Institute of Nuclear Physics, Novosibirsk, Russia

14:36 (PS1 P 03)
Visualization of a negative hydrogen ions beam in a vacuum insulation tandem accelerator
Timofey Bykov, Budker Institute of Nuclear Physics, Novosibirsk, Russia

14:42 (PS1 P 04)
Optimization of the beam shaping assembly and local protection of the accelerator source of epithermal neutrons
Tatiana Sycheva, Budker Institute of Nuclear Physics, Novosibirsk, Russia

14:48 (PS1 B 06)
PGNAA facility at RA-3: numerical approach towards first measurements of biological samples for BNCT
Lucas Provenzano, National Atomic Energy Commission (CNEA), Argentina

Poster Group II (Physics & Engineering)

13:30 (PS1 P 05)
Study of the potential application of low energy neutrons from neutron guides to BNCT radiosurgery
Pablo Torres, Universidad de Granada, Spain

13:36 (PS1 P 06)
Neutron control method for an accelerator-based BNCT system with a solid-state Li target
Satoshi Nakamura, Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

13:42 (PS1 P 07)
A High Flux Thermal Neutron Source for Small Animal Models for the Development of Drugs for Boron Delivery to Cancer Sites
Melvin Piestrup, Adelphi Technology, USA

13:48 (PS1 P 08)
Neutron Beams Optimization of Nuclear Medical Ship
Yizheng Chong, China Zhongyuan Engineering Corporation, China

13:54 (PS1 P 09)
Calculation of the response matrix of a PMMA cylindrical neutron spectrometer in consideration of angle distribution
Kentaro Baba, Graduate School of Biomedical Science and Engineering, Hokkaido University, Sapporo, Japan

14:00 (PS1 P 10)
Investigation of 124Sb-Be neutron source for BNCT.
Yoshinori Sakurai, Kyoto University, Japan

14:06 (PS1 P 11)
Investigation of beam component monitor for BNCT using gel detector
Yoshinori Sakurai, Kyoto University, Japan

14:12 (PS1 P 12)
Design of a model for BSA to meet free beam parameters for a 3.5 MeV linear accelerator
Kuo-Wei Lee, HEC Pharm Co., Ltd., China

14:18 (PS1 P 13)
Development of a treatment planning system for BNCT
Kuo-Wei Lee, HEC Pharm Co., Ltd., China

14:24 (PS1 P 14)
Quality assurance of an accelerator-based boron neutron capture therapy system: Dosimetric and mechanical aspects based on initial experience
Takahiro Kato, Southern Tohoku BNCT Research Center, Japan

14:30 (PS1 P 15)
Evaluation of a newly developed water-equivalent bolus technique in accelerator-based boron neutron capture therapy for skin tumors
Kazuhiro Arai, Southern Tohoku BNCT Research Center, Koriyama, Japan

14:36 (PS1 P 16)
Development of Thermal Neutron Moderator for Testing Boron Agents for Boron Neutron Capture Therapy (BNCT)
Go Ichikawa, Department of Physics, Graduate School of Science, Nagoya University, Nagoya, Japan

14:42 (PS1 P 17)
Patient-Position Monitoring System for BNCT Irradiation
Takushi Takata, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

Poster Group III (Radiation biology / Chemistry & Pharmacology)

13:30 (PS1 R 01)
Folate-modified cyclodextrin improves the intratumoral accumulation of existing boron compounds.
Yoshitaka Matsumoto, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

13:36 (PS1 R 02)
The role of GM-CSF during early cellular responses after BNCR and gamma irradiation
Lichao Chen, Division of Cell Signaling, Research Institute, and Division of Boron Neutron Capture Therapy, EPOC, National Cancer Center, Tokyo, Japan

13:42 (PS1 R 03)
188Re-liposome, a high energy beta-particle radiopharmaceutical shows enhanced efficacy on suppression of head and neck squamous cell carcinoma progression by repeated doses
Chun-Yuan Chang, Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taiwan

13:48 (PS1 R 04)
The combination effect of neutron irradiation and exposure to DNA-alkylating agent on glioblastoma cell lines with different MGMT and p53 status
Yuko Kinashi, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Osaka, Japan

13:54 (PS1 R 05)
Biological evaluation of boric acid uptake at different administration times. Comparative study between BPA and BA accumulation curves.
Agustina Portu, National Atomic Energy Commission (CNEA), Argentina

14:00 (PS1 R 06)
Overexpression of LAT1 by lipofection enhances BPA intracellular incorporation in glioblastoma cells
Ken Ohnishi, Department of Biol., Ibaraki Prefectural University of Health Sciences, Ibaraki, Japan

Daily Program

TUE 10 / 30

14:06 (PS1 R 07)
Radiolabeling and In Vivo Image Evaluation of Boron containing neuropeptide(NPY) analogue in breast cancer
Su-jung Chen, Division of Isotope Application, Institute of Nuclear Energy Research, Taoyuan, Taiwan

14:12 (PS1 R 08)
Disruption of Hif-1α enhances the sensitivity to BNCT in murine squamous cell carcinoma
Yu Sanada, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

14:18 (PS1 Ch 01)
Boron Tracedrugs: Drug-Design Challenge For Neutron Dynamic Therapy
Hitoshi Hori, Niigata University of Pharmacy and Applied Life Sciences, Higashijima, Akiha-ku, Niigata, Japan

14:24 (PS1 Ch 02)
Difference in BPA uptake between glioma stem cells and their cancerous cells
Fumiyo Yoshida, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Japan

14:36 (PS1 Ch 04)
In vitro studies of new boron-rich nanostructures for BNCT
Ignacio Porras, Universidad de Granada, Granada, Spain

14:42 (PS1 Ch 05)
Development of cyclic RGD-functionalized maleimide-containing closo-dodecaborate albumin conjugate (MID-AC) as an active tumor targeting boron carrier for neutron capture therapy
Kazuki Kawai, Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology, Yokohama, Japan

14:48 (PS1 Ch 06)
Gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs) for neutron capture therapy of cancer: Influence of particle size of Gd-nanoCPs on tumor-killing effect in vitro
Tooru Andoh, Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University, Kobe, Japan

15:00-16:00	**Parallel Session (Pa)**	**R1001, R1002, R1003**

Chemistry & Pharmacology (Ch2) — R1001

Chairpersons: Hiroyuki Michiue , Agustina Portu

15:00 (Pa Ch2 01)
New self-assembling peptide Drug Delivery System with BSH toward clinical application
Hiroyuki Michiue, Neutron Therapy Research Center, Okayama University, Japan

15:12 (Pa Ch2 02)
Development of closo-dodecaborate-containing water-soluble folate derivatives targeting to folate receptor α for boron neutron capture therapy
Shangze WU, Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology, Yokohama, Japan

15:24 (Pa Ch2 03)
Development of Boron-Containing Monosaccharide Derivatives for Boron Neutron Capture Therapy
Taiki Itoh, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan

15:36 (Pa Ch2 04)
Dodecaborate-sugar conjugates as delivery system for BNCT
Luigi Panza, Department of Pharmaceutical Sciences, Universita del Piemonte Orientale, Italy

15:48 (Pa Ch2 05)
Microfluidic technology for the synthesis of liposomes encapsulating boron compounds in Argentina
Agustina Portu, National Atomic Energy Commission (CNEA), Argentina

Radiation biology (R1) — R1002

Chairpersons: Veronica A. Trivillin, Aleksandr Kichigin

15:00 (Pa R1 01)
Hybrid gold and boron nanoparticles for treatment and boron dose estimation in boron neutron capture therapy for malignant glioma
Alexander Zaboronok, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

15:12(Pa R1 02)
Electroporation to optimize boron targeting for Boron Neutron Capture Therapy (BNCT): a study of boron biodistribution with Boric Acid in the hamster cheek pouch oral cancer model
Veronica A. Trivillin, National Atomic Energy Commission (CNEA), Argentina

15:36 (Pa R1 04)
Radiobiological in vitro and in vivo investigations on accelerator neutron source in Budker Institute of Nuclear Physics
Aleksandr Kichigin, Budker Institute of Nuclear Physics, Novosibirsk, Russia

Daily Program

TUE 10 / 30

Boron determination & Imaging technology (B2) — R1003

Chairpersons: Saverio Altieri, Zi-Zhu Zhang

15:00 (Pa B2 01)
Development of a prompt gamma ray imaging detector using LaBr3(Ce) scintillator and arrayed MPPC for Boron Neutron Capture Therapy
Keita Okazak, Graduate School of Engineering, Kyoto University, Kyoto, Japan

15:12 (Pa B2 02)
Uptake of p-borono-phenylalanine by brain tumor stem cells analyzed by mass cytometry
Natsuko Kondo, Particle Radiation Oncology Research Center, Institute for Integrated Radiation and Nuclear Science, Kyoto university, Osaka, Japan

15:24 (Pa B2 03)
Development of the electron tracking Compton camera for on-line imaging of 478 keV prompt gamma rays in BNCT
Tetsuya Mizumoto, Kyoto Space Gamma, Inc., Kyoto, Japan

15:36 (Pa B2 04)
Response of a CZT detector to the neutron and gamma radiation field of an accelerator based BNCT facility.
Setareh Fatemi, National Institute of Nuclear Physics INFN, Unit of Pavia, Via A. Bassi 6, IT-27100 Pavia, Italy

15:48 (Pa B2 05)
Exploring neutron autoradiography and alpha spectrometry techniques for boron measurements in bone.
Lucas Provenzano, Comision Nacional de Energia Atomica (CNEA), Argentina

16:00-16:20	**Coffee Break**	R1010

16:20-18:00	**Parallel Session (Pa)**	R1001, R1002, R1003

Physics & Engineering (P3) — R1001

Chairpersons: Andres J. Kreiner, Sara Gonzalez

16:20 (Pa P3 01)
Development of real-time neutron detector for beam quality discrimination measurement using LiCAF scintillator and neutron moderator
Michtaka Sato, Graduate School of Engineering, Kyoto University, Kyoto, Japan

16:32 (Pa P3 02)
Design of a BNCT irradiation room based on proton accelerator and Be target
Chiara Magni, National Institute of Nuclear Physics (INFN), Unit of Milan, Italy

16:44 (Pa P3 03)
Comparison of relative biological effectiveness (RBE) doses and the photon iso-effective dose model for predicting the normal tissue complication probability in boron neutron capture therapy (BNCT) of head and neck cancer patients
Hanna Koivunoro, Neutron Therapeutics Finland Oy, Helsinki, Finland

16:56 (Pa P3 04)
On the upper limit for the energy of epithermal neutrons for BNCT
Pablo Torres-Sanchez, Universidad de Granada, Spain

17:08 (Pa P3 05)
Computational assessment of BNCT neutron beams using radiobiological models
Lucas Provenzano, Comision nacional de energia atomica (CNEA), Argentina

17:20 (Pa P3 06)
How do photon iso-effective tumor doses derived from in-vitro BNCT studies compare to those from in-vivo cancer model data?
Sara Gonzalez, Comision nacional de energia atomica (CNEA), Argentina

17:32 (Pa P3 07)
Extension of the photon iso-ffective dose model to the dose-limiting normal tissues for BNCT of head and neck cancer
Sara Gonzalez, Comision nacional de energia atomica (CNEA), Argentina

17:44 (Pa P3 08)
Development of Real-Time BNCT Neutron Beam Monitor Using Thin Silicon Sensor
Masashi Takada, 1National Defense Academy of Japan

Clinical matter (Cl2) R1002
Chairpersons: Junichi Hiratsuka, Wolfgang Sauerwein

16:20 (Pa Cl2 01)
Boron neutron capture therapy for vulvar melanoma and extramammary Paget's disease of the genital regions
Junichi Hiratsuka, Department of Radiation Oncology, Kawasaki Medical School, Kurashiki, Japan

16:32 (Pa Cl2 02)
Reporting BNCT: A new approach towards an international standard
Wolfgang Sauerwein, BNCTeam, Department of Radiation Therapy, University Hospital Essen, University Duisburg-Essen (D), Germany

16:44 (Pa Cl2 03)
"Boron neutron capture therapy for malignant pleural mesothelioma: A case report"
Minoru Suzuki, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

16:56 (Pa Cl2 04)
Boron Neutron Capture Therapy for High-Grade Gliomas –Consolidating Published Evidence in One Place
Daniel Song Chiek Quah, Department of Radiation Oncology, National Cancer Center, Singapore, Singapore

17:08 (Pa Cl2 05)
First Patient from Singapore to Receive Boron Neutron Capture Therapy - Challenges Met and Lessons Learnt
Daniel Song Chiek Quah, Department of Radiation Oncology, National Cancer Center, Singapore, Singapore

17:20 (Pa Cl2 06)
Dosimetric Comparison of Boron Neutron Capture Therapy, Proton Therapy and IG-IMRT for Recurrent Anaplastic Meningioma
Daniel Song Chiek Quah, Department of Radiation Oncology, National Cancer Center, Singapore, Singapore

17:32 (Pa Cl2 07)
B-10 concentration kinetics in the tumor and blood in patients administered with BPA: a critical review
Hiroshi Fukuda, Department of Radiology, Tohoku Medical and Pharmaceutical University, Sendai, Japan8

17:44 (Pa Cl2 08)
How much does tumor location affect the treatment field size passively determined by a dose constraint to the mucosa in head and neck boron neutron capture therapy?
Katsumi Hirose, Department of Radiation Oncology, Southern Tohoku BNCT Research Center, Japan

Physics & Engineering (P4) R1003
Chairpersons: Yoshinori Sakurai, Hanna Koivunoro

16:20 (Pa P4 01)
Improvement of gamma-ray telescope system for BNCT at Kyoto University Reactor
Yoshinori Sakurai, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

16:32 (Pa P4 02)
Dosimetric influence of respiratory motion in boron neutron capture therapy for plumonary tumor
Ryoichi Hinoto, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan

16:44 (Pa P4 03)
e_LiBANS project: thermal and epithermal neutron sources based on a medical Linac
Valeria Monti, University of Turin and National Institute of Nuclear Physics, Turin, Italy

16:56 (Pa P4 04) **The influences of moderator geometry on beam quality of Li-target based AB-BNCT** **Wei-hua Lu**, Neuboron Medtech Ltd., Nanjing, China
17:08 (Pa P4 05) **A Simplification in BNCT Treatment Planning: Two-component Treatment of Inhomogeneous, Multi-component Dose Distributions, Based on Dose-Fraction Regularity** **Ryoichi Seki**, Research Center for Nuclear Physics, Osaka University, Japan
17:20 (Pa P4 06) **Evaluation of Multi-field Technique Applied to Boron Neutron Capture Therapy for Brain Tumors** **Shih-De Yoe**, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan
17:32 (Pa P4 07) **Status of BNCT Neutron Generator Development at the IAP RAS** **Vadim Skalyga**, Institute of Applied Physics of the Russian Academy of Sciences, Russia

Daily Program

Wednesday, October 31, 2018

CHANG YUNG-FA FOUNDATION International Convention Center

09:00-10:40	**Invited Lecture (IL4)** Chairpersons: Wen-Sheng Huang, Jun Hatazawa	**R 1001**
09:00-09:20 (IL4 01) **"Proposal of absolute biologic effectiveness (ABE) dose for boron neutron capture therapy (BNCT) -The effect of $^{10}B(n,\alpha)^{7}Li$ dose can be predicted by nucleo-cytoplasmic ratio or cell size "** **Koji Ono**, Osaka Medical College / Kansai BNCT Medical Center, Japan		
09:20-09:40 (IL4 02) **Neutron source for neutron capture therapy** **Hiroaki Kumada**, University of Tsukuba, Faculty of Medicine, Japan		
09:40-10:00 (IL4 03) **BNCT Combined with Nuclear Medicine Theranostics with Astatine-211** **Jun Hatazawa**, Osaka University Graduate School of Medicine/ Department of Nuclear Medicine and Tracer Kinetics, Japan		
10:00-10:20 (IL4 04) **CNAO, the Italian National Centre for Oncological Hadrontherapy: protons, carbon ions and the BNCT project for a comprehensive clinical approach to tumour treatments** **Sandro Rossi**, Fondazione CNAO, Italy		
10:20-10:40 (IL4 05) **Boron neutron capture therapy combined with early successive bevacizumab treatments for recurrent malignant gliomas** **Shin-Ichi Miyatake**, Osaka Medical College/Cancer Center, Japan		

10:40-11:00	**Coffee Break**	**R 1010**

11:00-11:50	**Plenary Lecture - Clinical matters (PL CI2)** Chairpersons: Hiroshi Fukuda, Yi-Wei Chen	**R 1001**
11:00-11:15 (PL CI2 01) **Fundamental and pioneering achievements in basic and clinical study for BNCT** **Hiroshi Fukuda**, Tohoku Medical and Pharmaceutical University/ Radiology, Japan		
11:15-11:30 (PL CI2 02) **Treatment outcome of recurrent meningioma, diffuse intrinsic pontine glioma, recurrent extracranial rhabdomyosarcoma, and recurrent inverted papilloma** **Yuan-Hung Wu**, Taipei Veterans General Hospital/ Oncology, Taiwan		
11:30-11:45 (PL CI2 03) **Initial experience of using a hybrid PET/MRI scanner for FBPA-PET** **Ko-Han Lin**, Department of Nuclear Medicine, Taipei Veterans General Hospital, Taiwan		

11:45-12:00 (PL CI2 04) **Salvage BNCT is an effective treatment option for recurrent high grade gliomas** **Yi-Wei Chen, Department of Oncology, Taipei Veterans General Hospital, Taiwan**

12:30-18:00	**Technical Tour to THOR**	
18:30-21:00	**Congress Banquet**	

Daily Program

Thursday, November 1, 2018

CHANG YUNG-FA FOUNDATION International Convention Center

09:00-10:30	**Plenary Lecture –Radiation biology / Physics & Engineering** Chairpersons: Yuan-Hao Liu , Mitsuko Masutani	**R 1001**

09:00-09:15 (PL R 01)
Effect of the change in a reactor power on the response of murine solid tumors in vivo, also referring to that in quiescent tumor cells, and its clinical significance in boron neutron capture therapy (BNCT)
Shin-ichiro Masunaga, Particle Radiation Biology, Division of Radiation Life Science, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan.

09:15-09:30 (PL R 02)
The therapeutic efficacy and radiobiological effects of boric acid-mediated BNCT in a VX2 multifocal liver tumor-bearing rabbit model
Fong-In Chou, BNCT Research and Development Consultant, Nuclear Science and Technology Development Center (NSTDC), National Tsing Hua University (NTHU), Taiwan

09:30-09:45 (PL R 03)
The biological properties of BNCR and accelerator-based BNCT system installed in NCC
Mitsuko Masutani, Nagasaki University/ Dept. Frontier Life Sci., Grad. Sch. Biomed. Sci., National Cancer Center Research Institute, Japan

09:45-10:00 (PL R 04)
Using Promoters of Granzyme B or NF-κB driven reporter genes combined with Multimodalities of Molecular Imaging for Theranostics of BNCT
Jeng-Jong Hwang, National Yang-Ming University/Biomedical Imaging and Radiological Sciences, Taiwan

10:00-10:15 (PL P2 01)
Some open problems for the improvement and the expansion of BNCT
Ignacio Porras Sánchez, Department of Atomic, Molecular & Nuclear Physics, University of Granada, Spain

10:15-10:30 (PL P2 02)
The Design of the Xiamen Humanity Hospital BNCT Center
Yuan-Hao Liu, Dept. of Nuclear Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing, China

10:30-10:50	**Coffee Break**	**R1010**

10:50-12:05	**Plenary Lecture – Miscellaneous /Chemistry & Pharmacology** Chairpersons: Kazuyo Igawa, Yung-Jen Chuang	**R 1001**

10:50-11:05 (PL M 01)
In vivo Evaluation system for accelerator-based Boron Neutron Capture Therapy
Kazuyo Igawa, J Okayama University Neutron Therapy Research Center, Japan

11:05-11:20 (PL M 02)
Zebrafish as a cancer model system for neutron capture therapy research
Yung-Jen Chuang, Department of Medical Science, National Tsing Hua University, Taiwan

11:20-11:35 (PL Ch 01)
Bio-distribution of Boron-containing Oligopeptide/Depsipeptide Analogs using DAHMI Tagging System
Po-Shen Pan, Department of Chemistry, Tamkang University, Taiwan

11:35-11:50 (PL Ch 02)
In Vivo Imaging Evaluation of a Neuropeptide (NPY) Derivative Containing Boron-rich for Breast Tumor Therapy
Ming-Hsin Li, Institute of Nuclear Energy Research, Taiwan

11:50-12:05 (PL Ch 03)
Cellular uptake of BPA: homogeneous or heterogeneous in a population of cells
Jen-Kun Chen, Institute of Biomedical Engineering & Nanomedicine, National Health Research Institutes, Taiwan

12:05-12:20 (PL Ch 04)
Synthetic study on [^{18}F]–L-2-fluoro-4-boronophenylalanine (^{18}FBPA), a theranostic compound in BPA BNCT, by "F minus method"
Mitsunori Kirihata, OPU Research Center for BNCT, Japan

12:10-13:00	**Lunch**
13:00-14:00	**Election Board Coun.**

14:00-15:30	**Poster Viewing & Presentation 2 (PS2)**	**R1010**

Poster Group I (Clinical matters / Miscellaneous / Physics & Engineering)

14:00 (PS2 Cl 01)
Preliminary study of the impact on dose distribution due to the reproducibility of shoulder position in sitting-positioned BNCT for head and neck cancer
Ryohei Kato, Southern Tohoku BNCT Research Center, Koriyama, Fukushima, Japan

14:06 (PS2 Cl 02)
Impact of inter-observer variability for mucosal delineation on the dosimetry of boron neutron capture therapy for head and neck cancer
AkihikoTakeuchi, Southern Tohoku BNCT Research Center, Koriyama, Fukushima, Japan

14:12 (PS2 Cl 03)
Study on application of BNCT to synovial sarcoma
Takuya Fujimoto, Department of Orthopedic Surgery, Hyogo Cancer Center, Akashi, Japan

14:18 (PS2 Cl 04)
Treatment of Major Cervical Artery Invasion of Head and Neck Cancer with Boron Neutron Capture Therapy
Masatoshi Ohmae, Oral and Maxillofacial Surgery, Rinku General Medical Center, Japan

14:24 (PS2 M 01)
Current Status of Neutron Capture Therapy in Colombia
Jose Sarta Fuentes, Physics Department, Pontificial Javeriana University, Bogota, Colombia

14:30 (PS2 M 02)
Treatment Result of Combined Volumetric-Modulated Arc Therapy (VMAT) and Simultaneously Integrated Inner-escalated Boost (SIEB) Radiotherapy in a Patient with Locally Advanced Maxillary Sinus Carcinoma.
Li-Wen Huang, Department of Radiation Oncology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan

14:36 (PS2 M 03)
Pilot study of Gadolinium Accumulation in Tumour with Intra-arterial Administration of Gadoteridol-Entrapped Water-in-Oil-in-Water Emulsion in VX-2 Rabbit Hepatic Cancer Model for Neutron Capture Therapy
Masashi Yanagawa, Department of Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Hokkaido, Japan

14:42 (PS2 P 01)
Neutron field characterization for Neutron Capture Therapies
Marine Herv, Laboratory of Subatomic Physics & Cosmology, Grenoble, France

14:48 (PS2 P 02)
Monte Carlo simulation-based design for an electron-linac-based neutron source for boron neutron capture therapy
Fujio Hiraga, Division of Quantum Science and Engineering, Graduate School of Engineering, Hokkaido University, Japan

14:54 (PS2 P 03)
Measurement of gamma-ray dose and neutron activation in BNCT beams using TLD-200
Wen-Chyi Tsai, Institute of Nuclear Engineering and Science, National Tsing Hua University, Hsinchu, Taiwan

15:00 (PS2 P 04)
Evaluation of neutron measurement system utilizing a LiCAF scintillator - optical fiber detector
Kazuhiko Akita, Osaka Medical College, Kansai BNCT medical center, Japan

15:06 (PS2 P 05)
Installation of accelerator-based BNCT system at Kansai BNCT Medical Center
Kazuhiko Akita, Osaka Medical College, Kansai BNCT medical center, Japan

Poster Group II (Physics & Engineering)

14:00 (PS2 P 06)
Rotary Type Beam profile monitor for Accelerator-Driven BNCT System
Keisuke Abo, Nagoya University, Nagoya, Japan

14:06 (PS2 P 07)
Design of Neutron Moderation Assembly for A-BNCT
Sung Gyun Shin, Division of Advanced Nuclear Engineering, POSTECH, Pohang, Korea

14:12 (PS2 P 08)
Results of the measurements of the 33S(n,α)30Si cross-section at CERN and ILL: application to NCT
Javier Praena, University of Granada, Spain

14:18 (PS2 P 09)
Advances of the Characterization of Neutron Capture by Boron and Gadolinium Using Geant4
Jose A. Sarta, Physics Department, Pontificia Universidad Javeriana, Bogota, Colombia

14:24 (PS2 P 10)
Accelerator based BNCT system in Nagoya University -Development of a sealed lithium target-
Sachiko Yoshihashi, Graduate School of Engineering, Nagoya University, Nagoya, Japan

14:30 (PS2 P 11)
Beam Dosimetry Equipment for the Nubeam BNCT Suite at Helsinki University Hospital Cancer Center
Iiro Auterinen, Neutron Therapeutics Finland Oy, Helsinki, Finland

14:36 (PS2 P 12)
High-accuracy measurement of the epithermal neutron flux of a 7Li(p,n)7Be-based BNCT neutron source with activation monitors
Xingcai Guan, School of Nuclear Science and Technology, Lanzhou University, Gansu, China

14:42 (PS2 P 13)
Neutron Photon irradiation damage analysis of human tissue for BNCT based on Geant4
Xiaoping Zhou, China Institute of Atomic Energy, Beijing, China

Daily Program

15:00 (PS2 P 16)
The Physical Design of a Modular Neutron Source Assembly for BNCT
Wei Zhang, Department of Reactor Engineering and Technology, China Institute of Atomic Energy, Beijing, China

15:12 (PS2 P 18)
Physical Design of Modular Neutron Source Device for AB-BNCT
Yan Li, China Institute of Atomic Energy, China

Poster Group III (Radiation biology / Chemistry & Pharmacology)

14:00 (PS2 R 01)
Biodistribution of Boric Acid (BA) and Boronphenyalanine (BPA) for BNCT in the hamster cheek pouch oral cancer model
Veronica A. Trivillin, National Atomic Energy Commission, Argentina

14:06 (PS2 R 02)
Optimization of The Classical Chemical Cancerization Protocol in the Hamster Cheek Pouch to Study BNCT for Oral Cancer
Andrea Monti Hughes, National Atomic Energy Commission, Argentina

14:12 (PS2 R 03)
Novel Oral Cancer & Precancer Experimental Model for Simultaneous Long Term Evaluation of the Effect of BNCT on Tumors and Precancerous Tissue
Andrea Monti Hughes, National Atomic Energy Commission, Argentina

14:18 (PS2 R 04)
Radiotoxicity Induced by BNCT Mediated by BPA: A Comparative Analysis in an Oral Cancer Model Employing Three Different Cancerization Protocols
Andrea Monti Hughes, National Atomic Energy Commission, Argentina

14:36 (PS2 R 07)
Investigation of the biological properties of neutron beam of accelerator-based BNCT system with intestinal crypt regeneration and ICP-AES
Shoji Imamich, Division of Boron Neutron Capture Therapy, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Tokyo, Japan

THU 11 / 1

14:42 (PS2 R 08)
Influence of oxygen status on therapeutic effect of boron neutron capture therapy in human tumor cells
Takaomi Harada, Southern Tohoku BNCT Research Center, Koriyama, Fukushima, Japan

14:48 (PS2 Ch 01)
Boron-rich oil-in-water emulsions as drug nanocarriers for boron neutron capture therapy
Krishna Reddy Pulagam, Radiochemistry and Nuclear Imaging, CIC biomaGUNE, San Sebastian, Spain

14:54 (PS2 Ch 02)
Functional evaluation of kojic acid-modified carborane developed as a boron drug for melanoma BNCT
Satoshi Dowaki, Graduate School of Engineering, Osaka City University, Japan

15:00 (PS2 Ch 03)
Development of S-Alkyl-closo-Dodecaborate-Containing Amino Acids as Boron Carrier for BNCT
Yoshihide Hattori, Research Center for Boron Neutron Capture Therapy, Osaka Prefecture University, Japan

15:06 (PS2 Ch 04)
Preparation methods of liposome which encapsulated boron compound at high concentration and efficiency.
Makoto Shirakawa, Department of Pharmaceutical Sciences, University of Fukuyama, Hiroshima, Japan

15:12 (PS2 Ch 05)
Development of boron-loaded Microbubbles for Focused Ultrasound Triggered Brain Tumor Drug Delivery
Ta-Wei Wang, Department of Biomedical Engineering and Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan

15:24 (PS2 Ch 06)
Synthesis and investigation of carborane coumarins as potential agents for BNCT
Ilya Korolkov, The Institute of nuclear physics, Astana, Kazakhstan

15:30 (PS2 R 09)
Evaluation of beta-emitting devices as a complementary tool of BNCT for the treatment of superficial cancer
Sara Gonzalez, Comision Nacional de Energia Atomica (CNEA), Argentina

15:36 (PS2 R 10)
In vitro studies of the DNA damage response (DDR) induced by BNCT
Sara Gonzalez, Comision Nacional de Energia Atomica (CNEA), Argentina

15:30-15:50	**Coffee Break**	**R1010**

15:50-17:00	**Parallel Session (Pa)**	**R1001, R1002, R1003**

Physics & Engineering (P5) — **R1001**
Chairpersons: Ignacio Porras Sanchez, Jia-Cheng Lee

15:50 (Pa P5 01)
Computational evaluation of dose distribution including radiation exposure to ambient organs for BNCT treatment combined with X-ray therapy or proton beam therapy
Kenta Takada, Faculty of Medicine, University of Tsukuba, Japan

16:02 (Pa P5 02)
Accelerator Based Neutron Capture Therapies in France
Daniel Santos, LPSC, Université Grenoble-Alpes, Grenoble, France

16:14 (Pa P5 03)
BNCT Facility at Maria Reactor – Final Kick-Off: Beam Test, Opening Research Station, Construction of Building for Reactor Laboratory for Biomedical Research and Progress in Formulation Programme of "Neobor" Scientific Platform
Michal Gryzinski, National Centre for Nuclear Research, Otwock, Poland

16:26 (Pa P5 04)
Comparison of Shielding Calculation Methods for an AB-BNCT Facility Based on the Be(p,xn) Reaction with 30 MeV Protons
Bo-Lun Lai, Institute of Nuclear Engineering and Science, National Tsing Hua University, Hsinchu, Taiwan

16:38 (Pa P5 05)
Opportunities for therapeutic beam monitoring with single-moderator spectrometers
Roberto Bedogni, INFN-LNF (Frascati National Laboratories), Frascati, Italy

Radiation biology (R2) — **R1002**
Chairpersons: Masao Fukumura, Maria Pedrosa-Rivera

15:50 (Pa R2 01)
5-aminolevulinic acid can sensitize malignant glioma to boronophenylalanine-based boron neutron capture therapy
Masao Fukumura, Department of Neurosurgery and Endovasucular Neurosurgery, Osaka Medical College, Japan

16:02 (Pa R2 02)
Evaluation of folate receptor targeted novel boron compound for boron neutron capture therapy using rat brain tumor model
Takuya Kanemitsu, Department of Neurosurgery, Osaka Medical College, Takatsuki-shi, Osaka, Japan

16:14 (Pa R2 03)
Radiobiology experiments for thermal and epithermal RBE factors in BNCT
Maria Pedrosa-Rivera, Universidad de Granada, Granada, Spain; Institut Laue-Langevin, Grenoble, France

Chemistry & Pharmacology (Ch3) — R1003
Chairpersons: Zhibo Liu, Po-Shen Pan

15:50 (Pa Ch3 01)
A novel boron-derived tyrosine serves as a theranostic agent for positron emission tomography and boron neutron capture therapy
Zhibo Liu, College of Chemistry and Molecular Engineering, Peking University, Beijing, China

16:02 (Pa Ch3 02)
Rational Designed Boronated Porphyrin Loaded Micelle Meet the Shortcoming of Small Molecule Boron Agents for Boron Neutron Capture Therapy
Zhibo Liu, College of Chemistry and Molecular Engineering, Peking University, Beijing, China

16:14 (Pa Ch3 03)
An innovative therapeutic approach for malignant mesothelioma treatment based on the use of Gd/Boron multimodal probes for MRI guided BNCT
Simonetta Geninatti Crich, Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy

17:00-18:00	**General Assembly**	R1001

Friday, November 2, 2018
CHANG YUNG-FA FOUNDATION International Convention Center

09:00-10:30	**Parallel Session (Pa)**	R1001, R1002, R1003

Physics & Engineering (P6) — R1001
Chairpersons: Iiro Auterinen, Hong-Ming Liu

09:00 (Pa P6 01)
Recent Development of BSA in D-BNCT
Jianfei Tong, Institute of High Energy Physics (IHEP), Chinese Academy of Sciences (CAS) Beijing, China

09:12 (Pa P6 02)
D-BNCT Project in China
Shinian Fu, Dongguan Neutron Science Center, Dongguan, China

09:24 (Pa P6 03)
Study of neutron production and moderation for Sulfur Neutron Capture Therapy
Guozhu He, Key Laboratory of Nuclear Data, China Institute of Atomic Energy, Beijing, China

09:36 (Pa P6 04)
Compact Accelerator-Driven BNCT System Used Sealed Lithium Target
Kazuki Tsuchida, Graduate School of Engineering, Nagoya University, Nagoya, Japan

09:48 (Pa P6 05)
Current Status of Research and Development Boron Neutron Capture Therapy in Indonesia
Widarto Widarto, Particle and Physics Division, Centre for Accelerator Science and Technology, National Nuclear Energy Agency, Yogyakarta, Indonesia

Radiation biology (R3) — R1002
Chairpersons: Andrea Monti Hughes, Veronica A. Trivillin

09:00 (Pa R3 01)
Biodistribution Studies of Maleimide-Functionalized Closo-Dodecaborate Albumin Conjugates (Mid:Bsa)iIn the Hamster Cheek Pouch Oral Cancer Model
Andrea Monti Hughes, National Atomic Energy Commission (CNEA), Argentina

09:12 (Pa R3 02)
Evaluation of the Radioprotective Effect of Oligo-Fucoidan to Reduce Dermatitis and Mucositis Induced by BNCT in Oral Cancer and Ectopic Colon Cancer Models
Andrea Monti Hughes, National Atomic Energy Commission (CNEA), Argentina

09:24 (Pa R3 03)
Boron Neutron Capture Therapy (BNCT) Combined with Bcg as Immunotherapy in an Ectopic Colon Concer Model: Local and Abscopal Effects
Veronica A. Trivillin, National Atomic Energy Commission (CNEA), Argentina

09:48 (Pa R3 05) **Dynamic Infrared Imaging for Biological and Preclinical Studies in BNCT** **Gustavo A. Santa Cruz**, National Atomic Energy Commission (CNEA), Argentina	
Boron determination & Imaging technology (B3) Chairpersons: Jen-Kun Chen, Ian Postuma	**R1003**
09:00 (Pa B3 01) **Intra cellular boron distribution evaluation by neutron autoradiography** **Ian Postuma**, Istituto Nazionale Di Fisica Nucleare (INFN), Unit of Pavia, Italy	
09:12 (Pa B3 02) **Use of EpiskinTM to evaluate BNCT radiation damage to healthy tissue** **Ian Postuma**, Istituto Nazionale Di Fisica Nucleare (INFN), Unit of Pavia, Italy	
09:24 (Pa B3 03) **Prompt gamma tomography for BNCT-SPECT: a feasibility study using a small animal phantom.** **Nicoletta Protti**, National Institute of Nuclear Physics INFN, Unit of Pavia, Pavia, Italy	

10:30-10:50	**Coffee Break**	**R1010**
10:50-11:30	**Closing Ceremony**	**R1001**
11:30-12:30	**Executive Board Meeting & Board of Councilors Meeting**	**R1006**

理未易察
Truth is not easy to be understood

International Congress on Neutron Capture Therapy
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Parallel Session

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Pa Cl1 01

Salvage Boron Neutron Capture Therapy (BNCT), Treatment Experiences of Recurrent Malignant Brain Tumors in Taiwan

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Introduction

Radiation therapy has an irreplaceable role in the modern oncologic therapy options, with advanced radiation techniques including Gamma knife radiosurgery, proton beam irradiation, carbon ion irradiation, had been developed in the past decades. However, there are still some limitations regarding radioresistant tumors, including glioblastoma, melanoma, and sarcoma. Hence, we have to focus on new treatment strategies to have a breakthrough in the next era of the field of radiation oncology. Boron Neutron Capture Therapy (BNCT) has a promising outcome treating glioblastoma with a significant increase in median survival year by several Japanese studies. It is a highly selective radiotherapy technique due to the high Tumor/ Normal tissue ratio of boronophenylalanine (BPA), the medication used for the BNCT treatment reaction.

Materials and Methods

In my presentation, I will introduce 3 treatment cases in Taiwan, the patient profile is as follows: 1.Case 2, a 35 years old woman with past history of right temporal insular anaplastic astrocytoma diagnosed in May, 2013. She received craniotomy and post operation CCRT (60Gy/30fx) with Temozolamide, but tumor recurrence was discovered during February, 2015. She received second craniotomy in July, 2015, which the surgical pathology showed Glioblastoma. She continued outpatient follow up, and BNCT was done on 2017/5/26. 2.Case 8, a 45 years old woman with the history of right mesial temporal brain tumor diagnosed in May, 2016. She received right anterior temporal lobectomy and hippocampectomy followed with post operation CCRT (59.4Gy/33fx) with Temozolamide. The pathology showed anaplastic astrocytoma, Ki-67=40. However, tumor recurrence was noted in August, 2017, with more extensive tumor evolvement including right posterior mesial temporal area, temporoparietooccipital area, and deep temporoparietal periventricular area. She received second craniotomy in September, 2017, which the surgical pathology showed Glioblastoma. She continued outpatient follow up, and BNCT was done on 2017/10/13. 3.Case 10, an 11 years old girl with genetic proven mismatch repair syndrome, MSH6 mutation positive. Multiple malignancy including right frontal glioblastoma, T lymphoblastic lymphoma, left posterior fossa medulloblastoma. Craniotomy and craniospinal irradiation and chemotherapy with cisplatin, vincristine, and cyclophosphamide was prescribed for medulloblastoma in December, 2012. Glioblastoma was discovered during February, 2015, while craniotomy and post operation CCRT was done immediately after diagnosis. BNCT was done on 2017/11/29, and the patient is currently under nivolumab (anti-PD 1 immunotherapy).

Results

Many patients with recurrent glioblastoma had significant tumor shrinkage after BNCT treatment. We will review more cases to evaluate the effectiveness of this tumor treatment option.

Conclusion

BNCT is effective for patients with malignant brain tumor, and has a significant effect on enhancing patient survival time while maintaining good life quality.

Keyword: boron neutron capture therapy, recurrent glioblastoma, mismatch repair syndrome

Pa Cl1 02

Results of phase 1 clinical trial of accelerator-based BNCT for recurrent malignant gliomas

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Introduction
Tumor selective particle radiation, boron neutron capture therapy is expected as a potential radiation modality for malignant tumors including malignant brain tumors. The biggest restriction of BNCT for universal and standard use as radiation therapy not only for malignant brain tumors but also for malignancies at other organs is the use of nuclear reactors. Another potential source of neutrons are the accelerator-based neutron sources currently being developed as neutron sources in hospital settings. Here we report the results of phase 1 clinical trial of accelerator-based BNCT for recurrent malignant gliomas.

Materials and Methods
The neutron source used in this clinical trial was a small cyclotron-based accelerator (BNCT 30, Sumitomo Heavy Industry, Japan). The boron compound used in this trial was BPA (SPM-011, Stella Pharma, Japan). The subjects of this trial were recurrent malignant gliomas (WHO grade III or IV) who had been treated with conventional XRT. The lesion should be one hemispherical supra-tentorial tumor. The study design was dose escalation consisting of 3 cohorts, as the prescribed dose of the scalp as 5.5, 7 and 8.5 Gy-Eq, respectively. The primary endpoint was safety and tolerability of the test subjects during the first 90 days after BNCT. The one of the secondary endpoint was the assessment of pharmacokinetics of BPA in the blood and urine. The other one was survival rate at 180 days after BNCT. Each cohort should be composed of 3 to 6 subjects. The first patient-in and last patient-in was 2012/11/14 and 2015/04/22, respectively. Totally 12 subjects (6 grade III and 6 grade IV) were enrolled.

Results and Discussion
Low (5.5 Gy-Eq) and high (8.5 Gy-Eq) scalp prescribed dose cohort was composed of 3 subjects. The numbers of subjects in intermediate cohort (7 Gy-Eq) needed to increase from 3 to 6, due to the occurrence of dose limiting toxicity (DLT), brain edema due to brain radiation necrosis. In every subjects in every cohorts, some adverse events (AEs) occurred. Most prominent AE possibly related to boron compound, SPM-011 was urinary tract obstruction caused by re-crystallization of BPA in urine. Most prominent AEs possibly related to BNCT were hair loss and transient increase of amylase. As severe AEs (SAEs), which caused the prolongation of admission or unscheduled admission of

subjects, epileptic seizure, brain edema, radiation necrosis occurred. The latter two were considered as DLT, however they subsided and were controlled by appropriate treatments. These AEs and SAEs were considered as not specific for this accelerator-based trial but as common even in reactor-based BNCT. Also these AEs and SAEs showed no tendency of increase in dose escalation. All cases survived more than 180 days after BNCT.

Conclusion
We could confirm the safety and tolerability up to 8.5 Gy-Eq as prescribed dose of the scalp in this phase 1 clinical trial. Now we are performing the phase 2 clinical trial to determine the efficacy of this new treatment modality using recurrent grade IV gliomas.

Keyword: accelerator, BNCT, phase 1 clinical trial, recuurrent malignant glioma

Pa Cl1 03

BNCT for Head and Neck Cancer : Summary of reactor irradiation.

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PURPOSE: Boron Neutron Capture Therapy (BNCT) is a form of radiation therapy that utilizes alpha rays from thermal neutron capture of the boron atom. Low energy thermal neutrons are easily taken up by the atomic nucleus and this probability is called the neutron capture cross-section (barn: 10-24 cm2). The thermal neutron capture cross-section for the stable isotope 10B is far larger at 3838 barns. The range of alpha particles and lithium recoil nuclei formed from fission reactions between the boron atom 10B and thermal neutrons is 9 mm and 5 mm, respectively, and this length is roughly equal to the diameter of a cell. In addition, the energy per unit length that each particle gives off to its surroundings before the particle stops, is called linear energy transfer (LET), and it is a high LET

radioactive beam. It has a large relative biological effect (RBE) of 2.5 to 5.0, and has a major cytotoxic effect against even radiation-resistant cells. Furthermore, this effect, unlike low LET radioactivity such as x-rays, is not influenced by the oxygen tension surrounding the cell, so it is highly effective against hypo-oxygenated cells that are resistant to low LET radioactivity. If this response occurs around cancer cells or in their reactive near-fields, the double strands in irreparable DNA break, causing cell death. Therefore, if boron atoms can be taken up into cancer cells, theoretically, those cancer cells alone would be selectively destroyed on a μm order. In this report, we summarize our clinical results for BNCT for the treatment of head and neck cancer at our institution.

METHODS: We started clinical studies for the treatment of head and neck cancer in 2003. Since then, we have completed the following four clinical studies: (1) an analysis of the accumulation of BPA in the tumor and surrounding normal -tissue using an 18FB-PA-PET study, (2) a BNCT clinical trial for recurrent head and neck cancer, (3) a BNCT clinical trial for head and neck melanoma, and (4) a BNCT clinical trial for newly diagnosed advanced head and neck cancer. All the patients provided consent, and the study was approved by the medical ethics committees of Kawasaki Medical School and Kyoto University. BNCT was performed, in a single fraction using an epithermal beam at the Kyoto University Research Reactor and the Japan Research Reactor 4.

RESULTS: The 18FBPA-PET study showed no difference in the T/N ratio between an SCC and a non-SCC group. Overall, 83% of the patients had a T/N ratio of more than 2.5. The response rates were more than 80% for all the BNCT clinical studies. Although mild alopecia, xerostomia, and fatigue were observed in all the patients, no severe adverse effects of grade 3 or higher occurred in these patient series.

CONCLUSIONS: Our preliminary results demonstrated that BNCT is a potentially curative therapy for patients with head and neck cancer. The treatment does not cause any serious adverse effects, and can be used regardless of whether the primary tumor has been previously treated.

Keyword: reactor, BNCT, Head and Neck, summary

Pa Cl1 04

Defining the molecular characteristics of boron compounds proposes the concept of precision medicine in BNCT field

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[Introduction]
Current BNCT, usually utilizing BPA as boron agent, is effective against melanoma and head/neck (HN) cancer, but is not always efficient for the other types of tumor such as glioblastoma. Retrospectively, this can be explained well by the results of transcriptome analyses showing that the expression levels of SLC7A5 (encoding LAT1 amino acid transporter: responsible for BPA uptake) are elevated in almost all cases of melanoma and HN cancer, but not in glioblastoma. This fact indicates that evidence-based development of boron agent is necessary to achieve the concept of precision medicine in BNCT field. To establish the basis, we need to understand: (1) the cellular and molecular mechanisms that underlie cancer properties of boron uptake, and (2) the intracellular determinants for pharmacokinetics of boron agent. By giving a cell-permeable BSH agent (OKD-002) as an example, we demonstrate that defining the molecular characteristics of boron agent allows us to establish the concept of precision medicine.

[Materials and Methods]
(1) Cellular uptake of OKD-002: To identify the cell-surface target protein of OKD-002, we began with the molecular profiling of the cells that were effectively, or ineffectively, induced with OKD-002, and found CD44 as a candidate. By biochemical and biological analyses, we validated that CD44 was interacted directly with OKD-002 and crucial for the uptake.
(2) Intracellular retention of OKD-002: OKD-002 localized at cytoplasm and the nucleolus, where translational machinery were actively built. By immunoprecipitation and loss-of-function studies, we revealed that OKD-002 was anchored to the translational machinery inside the cell.
(3) In silico analyses for the precision medicine: To provide the example of the precision medicine of BNCT, we analyzed TCGA glioblastoma datasets and found that CD44High cohort was frequently covered with SLC7A5Low cohort, indicating that OKD-002 could be useful for the patients who seemed unsuitable for BPA-based BNCT.

[Results]
First, we identified CD44 as a direct target of OKD-002. CD44 is a cell-surface glycoprotein that is predominantly expressed in several types of cancer. OKD-002 could be successfully delivered into CD44High, but not CD44Low cancer cells. Upon CD44 knockdown, the delivery efficiency was significantly reduced. In glioma model mice, OKD-002 was selectively delivered into CD44High glioma cells, not to CD44Low glioma cells, nor to the adjacent normal brain cells, either.
Second, we discovered the intracellular-retention machinery for OKD-002; the translational factors directly interacted with OKD-002 to retain it inside the cells. Mechanistically, eIF4A and eRF3 bind to poly-arginine peptide and PABPc1 binds to BSH molecule. Indeed, when these factors were overexpressed, the retention time of OKD-002 was prolonged. Importantly, we detected the selective decay of the translational machinery in the cells with OKD-002 and neutron-irradiation. This is peculiar to OKD-002-based treatment, and never observed in X-ray irradiation, even at the high-dose of 10Gy.
Third, we performed in silico analyses to show that OKD-002 could cover the patients who seemed unsuitable for BPA-based BNCT because of the low expression levels of SLC7A5. Our methodology is that the molecular profiling of patients' samples allows clinical doctors to determine the best protocol of BNCT: boron agents and the condition of neutron-irradiation.

[Conclusion]
Here, with OKD-002, we demonstrate that defining the molecular properties of boron agent provides the basis for the concept of precision medicine of BNCT. We emphasize the importance of the evidence-based development of boron agents that enables us to link the molecular profiling of cancer patients to the characteristics of boron agents. We believe that this paradigm shift can introduce the concept of personalized-medicine into BNCT research area.

Keyword: Precision medicine of BNCT, Poly-arginine BSH (OKD-002), CD44-dependent macropinocytosis of OKD-002,

Pa Cl1 05

Comparison between SUVmax, TNR, and TBR in 18F-BPA PET. Which index is correlated best with 18FDG uptake?

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Introduction: 18F-fluoro-boronophenylalanine positron emission tomography (18F-BPA PET) is used for determination of indication of boron neutron capture therapy (BNCT), but the institutions which can perform 18F-BPA PET examinations are still limited. This is why we have to make use of 18F-fluorodeoxyglucose (18FDG) PET as a screening tool before 18F-BPA PET. And it is reported that 18F-BPA uptake has a relatively good correlation with 18FDG PET uptake. The purpose of this study is to determine which index by 18F-BPA PET is correlated best with the index of 18FDG PET.

Materials and Methods: We performed a clinical trial with 120 participants between 2012 and 2018, which compared the images between 18F-BPA PET and 18FDG PET. Among these participants, patients with clinically uncontrolled and 18FDG PET-detectable tumors were selected, whose 18F-BPA PET indexes of tumor/normal ratio (TNR), tumor/blood ratio (TBR) and maximum standardized uptake value (SUVmax) were measured by a nuclear medicine physician, one of our authors (H.K.). Correlation factors of SUVmax of 18FDG PET to TNR, TBR, and SUVmax of 18F-BPA PET were compared. In addition, the correlations were further investigated with respect to the pathologies of the tumors, which were classified into adenocarcinoma, glioma, malignant melanoma, non-round cell sarcoma, round cell sarcoma, and squamous cell carcinoma.

Results: A total of 36 patients were selected for comparison of three 18F-BPA PET indexes. The indexes of those patients whose tumors were undetectable by 18F-BPA PET were regarded as 0. Correlation factors of 18FDG PET to TNR, TBR, and SUVmax of 18F-BPA PET were 0.6082, 0.5267, and 0.6633, respectively. SUVmax of 18F-BPA PET was correlated the best to SUVmax in 18FDG PET. After that, correlation factor of SUVmax of 18FDG PET and 18F-BPA PET were calculated from our data of 82 patients with measurable SUVmax of 18F-BPA PET. The correlation factor was 0.4624, and the regression line was $y = 0.2543*x + 1.9610$. The number of patients with adenocarcinoma, glioma, malignant melanoma, non-round cell sarcoma, round cell sarcoma, and squamous cell carcinoma were 23, 2, 7, 9, 13, and 27, respectively. When we investigated the correlations with respect to each pathology type, adenocarcinoma, glioma, round cell

sarcoma, and squamous cell carcinoma exhibited relatively similar correlations to that of the whole patients group. However, non-round cell sarcoma had a negative correlation of r = -0.1205. SUVmax in 18F-BPA PET of malignant melanoma patients were higher than those of other pathologies.

Conclusion: SUVmax of 18F-BPA PET was correlated best with SUVmax of 18FDG PET in general with a correlation factor of 0.4624 and a regression line of y = 0.2543*x + 1.9610. SUVmax of 18F-BPA PET had little correlation with SUVmax of 18FDG PET in patients with non-round cell sarcoma. Malignant melanoma patients exhibited higher SUVmax of 18F-BPA PET than expected from SUVmax of 18FDG PET, compared with other pathologies.

Keyword: BNCT, 18F-BPA PET, 18FDG PET

Pa B1 01

A virtual neutron anti-scatter grid for future Cd(Zn)Te based BNCT-SPECT systems

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Introduction: Prompt gamma-ray imaging in a SPECT like procedure is favored to realize patient imaging and dosimetry in boron neutron capture therapy (BNCT). Many of the proposed imaging systems employ CdTe or CdZnTe detectors due to their high quantum efficiency, good energy resolution and moderate cooling requirements. A downside of these two materials is their sensitivity to neutrons, which can interfere with the measurement of the prompt gamma signal from the boron neutron capture reaction. In a previous study we have demonstrated that this sensitivity can be used to generate a second, dependent signal that can also be used for imaging and dosimetric calculations in BNCT assuming that the read out electronics provides a photon counting operation mode. In SPECT, image quality can typically be increased by using collimators, or anti-scatter grids. These structures can effectively improve the spatial resolution and contrast for the 478\, keV photons that originate from the boron neutron capture reaction. Such devices, however, are difficult to construct for neutrons and they may produce secondary radiation that interferes with the signal from the boron neutron capture reaction.

Materials and Methods: In this study we use a stochastic modeling and an estimation approach that allows approximating a collimator function for the neutron signal of the CdTe detectors. We implement a sequential Monte Carlo (SMC) algorithm to determine the origin of the scattered neutrons in a phantom. We have tested the method on simulated data of a CdTe line detector and compared the spatial resolutions of the boron neutron and cadmium neutron capture reactions through simple image reconstructions of both reaction types.

Results: SMC algorithms allow determining the scatter location of neutrons within a phantom in BNCT. Great improvements on the spatial resolution of the neutron data can be achieved by exploiting the information from neutron scatter effects.

Conclusion: We present an approach to approximate the collimator functionality for scattered neutrons that can be detected, if Cd(Zn)Te detectors are used in BNCT-SPECT. The virtual collimator allows increasing the spatial resolution of the neutron signal, thus permitting image reconstruction also for the neutron signal.

Keyword: Cd(Zn)Te, promp gamma imaging, neutron imaging, anti-scatter grid, stochastic modelling

Pa B1 02

Boron analysis and imaging of 2hr-BPA-exposured cells by using micro proton particle induced gamma-ray emission (PIGE).

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Introduction

Boron Neutron Capture Therapy has been a particle radiotherapy and developed for treatment of malignancies. Boron existence and thermal neutron penetration into the target tissues are required. At present, p-boronophenylalanine was administrated intravenously, just before and during neutron irradiation to achieve high boron concentration and high tumor/normal tissue boron ratio in clinical research.

In this study, we used micro ion beam particle induced gamma-ray emission (PIGE) to confirm the boron distribution of immediate phase in vitro.

Material and methods
U251 human glioma cell line was used. 4m thin polycarbonate membrane ware treated with poly-L-Lysine Hydrobromide (PLL, Sigma Aldrich) as adhesive coatings that allow cells attach on the membrane. This membrane was set on special sample holder. Cell was cultured on it.
p-boronophenylalanine (BPA) (Interpharma PRAHA, a.s. Czech Republic), were used. BPA and fructose were dissolved as previously described. 160 and 800μg10B/mL BPA dissolved in culture medium were prepared.
After U251 cells attached on polycarbonate membrane and under the logarithmic growth phase, exchange the medium to BPA containing culture medium. Subsequent to 2hrs BPA exposure, medium was aspirated, and specimens were lyophilized. Medium-wash group had one more procedure of gentle wash twice with phosphate buffered Saline (PBS) after aspiration.
Micro particle-induced X-ray emission (PIXE) and micro particle-induced gamma-ray emission (PIGE) analysis was performed at Takasaki Ion Accelerators for Advanced Radiation Application (TIARA, Takasaki, Japan). It involves measurement of prompt gamma-ray at 428keV from 10B(p, p'γ)7Be. The freeze-dried cellular samples were mounted and took elements (Potassium, Phosphate and Boron) distribution images and whole spectrum. These data were analyzed using software named PIXEna, which developed by Takasaki Advanced Radiation Research Institute.

Results
The ratio of boron counts to total (%) was control group: 1.35±0.073%, 2hr boron exposure group:2.33±0.35%, boron exposure and wash group:1.58±0.095%. boron distribution image of boron exposure group was matched up with cellular element (P, S, K), but distribution image of boron exposure and wash group became invisible boron.

Discussion
We previously reported that boron had been detectable and could take 2-dimentional images using micro PIXE/PIGE. PIGE could detect 18μg10B/mL of f-BPA in the culture medium.
Yoshida et al (2002) reported that the cellular boron concentration was dependent on cell cycle and BPA exposure time. Increase tendency of boron concentration was revealed in the course of 24hours. The cells cultured with BPA solution of 60μg10B/mL for 3hrs, boron concentrations ware 0.5-1.0μg/107 cells.

Ono et al (1999) reported that 11.0 and 5.6 μg10B/mL of mean 10B concentrations in tumors were achieved 2-3hours after the administration of 1500 and 750 mg/kg body weight of BPA. This report used vivo-vitro colony formation assay, and it revealed concentration-dependent antitumor effects of BNCT.
In this method, only extra-cellular or peri-cellular 10B were detected, and cause controversy over previous reports. But It was limited condition such as in vitro, high concentration BPA dissolved in culture medium, attached cell, and lyophilization of specimen preparation may have certainly affects.

Conclusion
In vitro analyses of 2hrs, 800μg10B/mL BPA solution exposure, 10B exist extra-cellular or peri-cellular and were washed away after gentle maneuver.

Keyword: boron particle induced gamma-ray emission

Pa B1 03

Neutron autoradiography combined with UV-C sensitization: towards intracellular localization of boron

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Introduction
Our group has reported the imprint formation of biological material on polycarbonate nuclear track detectors (NTD) by UV-C exposure, as an approach to simultaneously visualize cell contours and nuclear tracks coming from the boron neutron capture reaction. A reduction in track density (fading) on sensitized polycarbonate foils was also reported by our group. In this work we present an improvement of the neutron autoradiography technique combined with UV-C sensitization of polycarbonate NTD with the aim to enhance spatial resolution of nuclear tracks etched pits respect to main cell structures or compartments, such as nucleus and cytoplasm. We focused our attention on reducing the UV-C irradiation time, achieving contrast enhancement of cells imprints while preserving nuclear track etched pits in a single image, thus avoiding the need of using image co-registration methods.

Materials and methods
Considering that cell nucleus has a higher UV absorption than cytoplasm and that haematoxylin has even higher UV absorption and preferentially stains nucleus, we proposed to enhance the contrast between this two main cell structures by means of haematoxylin staining before UV-C sensitization. Several experiments were performed in order to optimize UV-C exposure parameters together with etching conditions for cells imprints formation using the SKBR3 breast cancer cell line. Cells were cultured on polycarbonate detectors (LexanTM) and incubated with BPA-f. Cell attachment strategies, toxicity assays and boron incubation times were explored. The assemblies "cells+NTD" were irradiated with thermal neutrons at the RA-3 reactor. Regarding cell imprints, different parameters were also explored, such as: UV-C exposure times; haematoxylin staining before UV-C and staining times; and finally different etching times.

Results
Thus, we established the parameters of UV-C sensitization and chemical etching conditions that let us achieve clear images of cell imprints together with nuclear track etch pits in a single image. The proposed method improves significantly the resolution of the imprints images and allowed us to clearly differentiate the cell nucleus from the rest of the cell. Indeed, the optimized method even reproduces the findings in the stained cell culture, such as multinuclear cells or division processes in SKBR3 cell line. In addition, this method reduces the UV-C exposure time from 6 h (according to previous works) down to 5 min, which is an important experimental issue. This remarkable reduction in the exposure time would prevent fading of nuclear tracks.

Conclusion
It is fair to emphasize that this proposal involves no difficult experimental setup or complex image acquisition systems. The contrast enhancement was achieved just by adding the haematoxylin staining step previous to UV-C lamp exposure and, as in the "conventional" autoradiography technique, only a light microscope equipped with a digital camera is necessary. The proposed methodology can be applied to study the boron distribution independently of the chosen cell line and/or boron compounds. The obtained images together with details and discussion of the performed method will be presented.

Keyword: neutron autoradiography, UV-C sensitization, haematoxylin staining, NTD, cell imprints

Pa B1 04

Neutron autoradiography approaches to study microdistribution of boron compounds in a diffuse lung metastases experimental model

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Introduction: BNCT has been applied to treat non resectable lung metastasis. Our group has provided evidence of the therapeutic success of BNCT mediated with BPA in an experimental model of colon carcinoma diffuse lung metastases in BDIX rats. Boron determination at microscopic level is essential when considering a BNCT protocol. Several approaches employing neutron autoradiography with nuclear track detectors (NTD) have been developed in our group: (1) qualitative autoradiography (QLA), that implies irradiation with high neutron fluences and longer etching times, allowing the observation of boron microdistribution through differences in shades of grey; (2) quantitative autoradiography (QTA), that converts track density (number of tracks per unit area) measurements into absolute boron concentration values using a calibration curve; and (3) UV-C sensitization of polycarbonate (UVC-A) that produces an imprint of the biological material on the NTD, thus enhancing spatial resolution. They have been applied to different biological matrixes. In this work we present the particular set-up of these methodologies when applied to the analysis of normal lung tissue and metastatic lung cancer of BDIX rats.

Materials and methods: The normal lung of BDIX rats post-administration of different boron compounds (boric acid, GB-10 and BPA) was used to set-up the above mentioned techniques. Lung tissue with diffuse tumors was also analyzed. The tissue blocks were excised from the animals and stored in N2(liq) in order to prevent 10-B migration. The blocks were then sectioned in a cryostatic microtome at different nominal thicknesses. The sections were mounted on polycarbonate NTD foils and the assemblies were irradiated at the RA-3 reactor (CNEA). QTA and UVC-A samples were exposed to a 1012 cm-2 fluence whereas a fluence of 1013 cm-2 was selected for QLA. An irradiation step with UV-C was interposed between histological exploration and chemical etching. The tracks

were revealed with a KOH solution at 70ºC during 2 min (QTA) or 4 min (QLA and UVC-A).The autoradiographic images were explored according to the specific requirements of each technique and in the case of QTA, nuclear track density was quantified in order to obtain absolute boron concentration values.

Results: Lung sections were obtained at -20 ºC, so evaporation of the water contained in the sample occurred until the tissue reached ambient temperature. This evaporation process produces an increase in the boron concentration value that has to be taken into account through a correction factor (CEv). Moreover, the section thickness is reduced. Normal lung autoradiographies showed homogeneous boron distribution regardless of the boron compound administered. Conversely, QLA of lung with diffuse tumors (employing BPA as the boron compound) exhibited differences in shades of grey, revealing a preferential boron uptake of tumor areas in comparison with surrounding normal lung. QTA results showed a relation of about 2 between these structures. Well contrasted tissue imprints of lung sections were obtained with UVC-A under the established conditions. This analysis is being extended to samples from BDIX rats with diffuse lung tumors injected with a combination of BPA+GB-10. The global concentration values will be compared with ICP-OES results reported in previous works.

Conclusion: The different approaches of the autoradiographic technique were explored and optimized to be applied to samples of normal lung and lung with metastases. This technique is particularly useful to assess boron microdistribution in the case of diffuse tumors where gross boron content values can be particularly misleading. The information obtained through the autoradiographic analysis will contribute to the understanding of the radiobiology of the BNCT protocols under study.

Keyword: microdistribution, neutron autoradiography, boron imaging, NTD, polycarbonate

Pa B1 05

Single Cell ICP-MS: Quantification of Metal Content in Individual Cells - An Insight into Cancer Treatment

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Cancer therapy drugs are usually administered at high doses to have the desired effect on cancer cells; however this can lead to long and short term side effects, and cellular resistance to the drug. There is a need for targeted cancer therapy drugs to be developed. Boron neutron capture therapy (BNCT) is based on delivering boron-containing compounds, such as boronophenylalanine (BPA), to tumor tissue followed by thermal/epithermal neutron irradiation. Therefore, it is crucial to quantify the uptake of drugs to evaluate therapeutic effect of BNCT, for which ICP-OES and ICP-MS are usually employed to determine the boron concentration in cell, blood and tissues. In terms of cellular uptake of boron-containing compounds, traditional methods for investigating boron content consist of total digestion of the cell population, losing vital information on the mass of drug in individual cell and the percentage/number of cells containing the drug. We intend to present a new technique, Single Cell ICP-MS (SC-ICP-MS), which is capable of quantifying metal-containing drugs as well as boron-containing drugs. We use the uptake of the chemotherapy drug, cisplatin, into the resistant and non-resistant ovarian cancer cell lines (A2780 and A2780-CP70). The SC-ICP-MS analysis allowed for the quantitation of cisplatin, and other metals and non-metal elements (ex. Fe, Zn, Cu, B…etc.) within individual cell to generate information on mass and mass distribution in the particular cell population. This technique would be a useful tool in the development of targeted drugs giving fast and in-depth results on the amount of drug and drug distribution in cells that can be linked to biological cellular responses. Consequently, we foresee applications of SC-ICP-MS in research and development of novel drugs for neutron capture therapy.

Keyword: inductively coupled plasma-mass spectrometry (ICP-MS), single cell uptake, boron-containing compound

Pa Ch1 01

Metabolism-controlled boron delivery systems composed of p-boronophenylalanine and poly(vinyl alcohol)

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Introduction
p-Boronophenylalanine (BPA) is one of the most promising drugs for boron neutron capture therapy (BNCT) owing to its preferential accumulation within malignant tumors via a large amino acid transporter (LAT1), which has been reported to be overexpressed on many cancer cells. However, BPA cannot maintain high intracellular boron concentration for a long period when extracellular BPA concentration decreases, because LAT1 is an amino acid exchange transporter. Such efflux of BPA from the target cells compromises its therapeutic efficacy. Here, to slow down the efflux of BPA, we developed a novel boron delivery system composed of BPA and poly(vinyl alcohol) (PVA). The boron delivery system, termed PVA-BPA, is constructed by forming reversible bond between diol in PVA and boronic acid in BPA. This chemical structure exposes the phenylalanine structure that is recognized by LAT1, and is expected to induce multivalent interaction between BPA and LAT1, facilitating cellular uptake via LAT1-mediated endocytosis and prolonging intracellular retention of BPA by avoiding the aforementioned efflux. In this study, we examined these potentials of PVA-BPA for BNCT in in vitro and in vivo.

Materials and Methods
PVA was synthesized by reversible addition-fragmentation chain-transfer polymerization of vinyl acetate and subsequent hydrolysis. PVA-BPA was prepared by simple mixing of PVA and BPA in aqueous solution.
In cellular uptake study, BxPC3 cells were incubated with PVA-BPA in the presence or absence of a system L inhibitor, and the amount of intracellular boron was quantified using inductively coupled plasma mass spectrometry (ICP-MS). Subcellular distribution of PVA-BPA was observed using confocal laser scanning microscopy (CLSM) with fluorescent boron-sensor.
Biodistribution of PVA-BPA was evaluated in BALB/c mice bearing subcutaneous CT26 tumors and BALB/c nude mice bearing subcutaneous BxPC3 tumors. PVA-BPA was intravenously injected from the tail vein, and the amount of boron in tumors and organs was quantified using ICP-MS. Intratumoral distribution of PVA-BPA was also analyzed using CLSM. To investigate antitumor activity, PVA-BPA was intravenously injected to the CT26 tumor model, and neutrons were irradiated in Kyoto University Research Reactor (KUR).

Results
Cellular uptake of PVA-BPA was higher than the complex of fructose and BPA (fructose-BPA), and this efficient cellular uptake was markedly inhibited by the system L inhibitor. In addition, PVA-BPA could maintain high intracellular boron concentration even when extracellular BPA was removed. Also, CLSM revealed that PVA-BPA was localized mainly in lysosomes. These results indicate that PVA-BPA can be internalized into the cell through LAT1-mediated endocytosis, and improve the intracellular retention.
In in vivo study, PVA-BPA could selectively accumulate within both BxPC3 and CT26 tumors, and exhibited significantly higher intratumoral boron concentration compared with fructose-BPA 3 h and 6 h after injection. CLSM observation also illustrated that PVA-BPA could almost homogenously distribute in the target tumor. It should be noted that PVA-BPA could be efficiently excreted from the kidney; thus, boron concentration in blood and most of normal organs was lower than that in the tumor. Ultimately, PVA-BPA showed significantly higher antitumor activity than fructose-BPA.

Conclusion
PVA-BPA successfully slowed down the untoward efflux of intracellular BPA, maintained high intratumoral boron concentration, and exerted significantly enhanced antitumor activity even compared with conventional BPA. To the best of our knowledge, this is the first success in augmenting the therapeutic potential of BPA using functional polymers.

Keyword: boron delivery, BPA, functional polymer, LAT1

Pa Ch1 02

Preclinical study on boron neutron capture therapy for bone metastasis with human breast cancer cell lines

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Introduction: Breast cancer, the most morbid malignancy found in women, is frequently encountered in Japan. Although most breast cancer is diagnosed at an early stage, 20-30% of cases turn metastatic. Furthermore, about 70% of such cases metastasize to the bone. When systematic pharmacotherapy is not effective, the disease is difficult to control. Here, then, is where BNCT proffers the only option, presently, for resolving these problems. We have previously demonstrated the effectiveness of boron neutron capture therapy (BNCT) with the use of p-borono-L-phenyl-alanine (L-BPA) on tumors in the limbs of human CCS-bearing nude mouse models. In the present study, we established a bone metastasis model for breast cancer and investigated in vivo biodistribution of L-BPA and antitumor effects after BNCT in the bone metastasis model.

Materials and methods: MDA-MB-231-luc, a breast cancer cell line of human origin, was suspended in Matrigel®, injected into the tibia of the left hind leg of the nude mice. After 8 weeks, a tumor mass was observed in the tibia of the mice using a CT scan and luminescence imaging. With regard to 10B biodistribution study, BPA-fructose complex (BPA-Fr, 24 mg 10B/kg) was intravenously administered to the bone metastasis model of breast cancer. At a predetermined time after administration, the mice were sacrificed and blood and tissue samples were immediately collected. The concentration of 10B in the sample was then measured by ICP-AES. In the BNCT trial, the bone metastasis model of breast cancer was divided into a BNCT group and a control group. The tumors in the left hind legs were irradiated using thermal neutrons at the Institute for Integrated Radiation and Nuclear Science, Kyoto University.

Results: Bone metastasis was successfully produced in the human breast cancer-bearing animal model. The formation of a solid tumor mass formed in the left tibia was confirmed by macroscopic observation, micro-CT scans and luminescence imaging. Then, 1.5 hour after the BPA-Fr administration, the 10B concentration in the bone metastasis model tumor tissue reached 23 μg 10B/g wet tumor tissue. Tumor-to-blood and tumor-to-normal tissue (normal bone) ratios were 2.4 and 2.4, respectively, at the same time point. In BNCT trial, the growth of tumor mass was observed in the control group. In contrast, the BNCT group showed a suppressed tumor-growth with no damage to the normal bone. These results suggest that boron accumulates specifically in the bone tumor and that BNCT destroys tumor cells only at the site of the bone metastasis, preventing bone fracture.

Conclusion: The present studies indicate that BNCT using BPA-Fr can be a promising therapeutic option for the bone metastasis of breast cancer.

Keyword: Preclinical study, Bone metastasis, Breast cancer, p-borono-L-phenyl-alanine

Pa Ch1 03

Synthesis and radiolabelling (124I) of multifunctionalised gold nanorods (AuNRs) as boron drug delivery agents using a pretargeting strategy based on bioorthogonal 'click reaction' with application in Boron Neutron Capture Therapy.

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Introduction: Boron neutron capture therapy (BNCT) is a promising cancer treatment which exploits the neutron capture capacity and subsequent fission reaction of boron-10 (10B). One limitation of BNCT is the need to develop drugs that are able to deposit a sufficient number of 10B atoms specifically in tumour cells. In this work, we present the preparation of gold nanorods (AuNRs) containing surface-attached polyhedral heteroboranes and electron-deficient tetrazine derivatives, capable to undergo the bioorthogonal 'click reaction' in vivo with trans-cyclooctene (TCO)-conjugated antibodies (TCO-mAbs). Our aim is to accumulate boron-loaded AuNRs in the tumor using a pretargeting strategy, which has proven efficient to selectively accumulate imaging agents in tumors but has never been applied in therapeutic studies. Radiolabelling of both the TCO-mAbs and the functionalized AuNRs was carried out to enable in vivo visualization of both species using Positron Emission Tomography (PET) imaging. Preliminary studies in wild type animals have been carried out.

Materials and Methods: The thiolated derivatives of cobalt bis(dicarbollide) and tetrazine, required for attachment to the AuNRs, were first prepared. The thiolated cobalt bis(dicarbollide) derivative was synthesized by treatment of cobalt bis(dicarbollide) with tetrahydropyran (THP) and subsequent reaction with potassium thioacetate. The thiolated electron-deficient tetrazine derivative was prepared by first synthesizing 3-(5-aminopyridin-2-yl)-6-(pyridin-2-yl)-s-tetrazine, which was reacted with S-(6-chloro-6-oxohexyl) ethanethioate. Both compounds were hydrolyzed before the preparation of functionalized AuNRs, which was achieved following a seed-mediated growth method. Characterization of the AuNRs was carried out by transmission electron microscopy (TEM, size determination) and X-ray photoelectron spectroscopy (XPS, determination of the relative amount of boron). Radiolabeling of the AuNRs was finally achieved by absorption of 124I- on the surface of the gold core. TCO and deferoxamine (DFO, to enable radiolabelling with 89Zr) were attached to lysine residues of the mAbs following established methods. Ra-

diolabelling with 89Zr was achieved by incubation with 89Zr(C2O4)2. Biological activity of the functionalized and labeled mAbs was confirmed with cell binding assays. Preliminary in vivo studies with labeled AuNRs to assess biodistribution and circulation time were conducted in wild type mice.

Results: The (protected) thiolated cobalt bis(dicarbollide) and tetrazine derivatives could be obtained in overall yields of 70% and 65%, respectively. Uniform and stable AuNRs functionalised simultaneously with tetrazine units, cobalt bis(dicarbollide) and polyethylene glycol (for stabilization) were obtained. Average size was 10x30 nm as demonstrated by TEM. Close-to-quantitative labelling efficiencies were achieved by incubation with 124I-. The mAbs were successfully functionalised with both TCO and DFO. Cell binding assays showed preservation of binding capacity to their receptors (in our case with the antibody Trastuzumab to HER2 receptors). In vivo studies performed with the labelled AuNRs showed significant accumulation in the liver early after intravenous administration, although circulation time is sufficient to approach further studies in tumour-bearing animals. These studies, together with evaluation of the efficacy of the pretargeting strategy, are currently ongoing.

Conclusions: Multifunctionalized radiolabelled AuNRs can be easily prepared following the described method. The combination of these outstanding nanosystems with TCO-functionalized mAbs using a pretargeting strategy might become the perfect strategy to selectively accumulate a sufficient amount of boron atoms in tumors.

Keyword: BNCT, boron-delivery, pretargeting, gold-nanorods, PET-imaging

Pa Ch1 04

Enhanced tumor-targeted delivery of p-boronophenylalanine using fructose-functionalized polymers for boron neutron capture therapy

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Parallel Session

Introduction

Boron neutron capture therapy (BNCT) is a minimally invasive cancer therapy that utilizes nuclear fission reaction of thermal neutrons and boron. Currently, p-boronophenylalanine (BPA) is one of the most extensively investigated agents in clinical trials of BNCT, because it can be preferentially taken up through the L-type amino acid transporter (LAT1) overexpressed on many cancer cells. However, poor water-solubility of BPA deteriorates usability, demanding use of solubilizer including fructose and sorbitol. In addition, since LAT1 is an amino acid-exchange transporter, BPA is excreted from the cancer cells when extracellular BPA concentration is decreased. Thus, BPA cannot retain in cancer cells for a longitudinal period and may compromise the therapeutic efficacy.

In this research, to improve the retention of BPA in the cancer cells, we synthesized poly(ethylene glycol)-poly(L-lysine) (PEG-PLys) block copolymers functionalized with fructose molecules that have strong affinity to BPA. The synthesized polymer, termed PEG-PLys(fructose), possesses high water-solubility, and the fructose molecule in the polymer can reversibly form complex with BPA, thereby improving BPA solubility in aqueous solution. In addition, the PEG-PLys(fructose)-BPA complex is expected to induce multivalent interaction with LAT1 transporters, and be taken up by cancer cells through endocytosis. By changing the pathway of cellular, PEG-PLys(fructose)-BPA should avoid the rapid clearance from the cells via LAT1, and prolong the intracellular retention. Here we report the promising potential of PEG-PLys(fructose)-BPA for BNCT.

Materials and methods

(1) Synthesis of PEG-PLys(fructose)

To synthesize PEG-PLys(fructose), 2, 3, 4, 5-di-O-isopropylidene-beta-D-fructopyranose was introduced to the PEG-PLys via a carbamate linkage, and acetal groups were deprotected to produce PEG-PLys(fructose).

(2) Preparation of PEG-PLys(fructose)-BPA

PEG-PLys(fructose)-BPA complexes were prepared by simple mixing of PEG-PLys (fructose) and BPA in aqueous solution and adjustment of pH.

(3) in vitro study

To investigate cellular uptake of PEG-PLys(fructose)-BPA, BxPC3 cells overexpressing LAT1 were incubated with PEG-PLys(fructose)-BPA for 3h, and the amount of 10B was measured by ICP-MS. To examine selectivity to LAT1, system L inhibitor was also used in this experiment. Cellular internalization pathway of PEG-PLys(fructose)-BPA was investigated using confocal laser scanning microscopy (CLSM) with a fluorescent probe for BPA.

(4) in vivo study

Biodistribution of systemically administered PEG-PLys(fructose)-BPA in subcutaneous mouse tumor models was examined using ICP-MS, and intratumoral distribution of PEG-PLys(fructose)-BPA was observed by CLSM. For the study of tumor suppression, thermal/epithermal neutrons were irradiated to tumors 3 and 6 hours after intravenous injection of polymer-BPA.

Results
PEG-PLys(fructose) with narrow molecular weight distribution was synthesized successfully (Mw of PEG: 10, 000, polymerization degree of PLys: 57, fructose introduction rate: 57.8 %), and it augmented the water-solubility of BPA.
The cellular uptake of PEG-PLys(fructose)-BPA was higher than conventional boron drug, and was decreased by 54% upon addition of system L inhibitor, suggesting that PEG-PLys(fructose)-BPA can target LAT-1 and be efficiently taken up by the cancer cells. CLSM study showed that the polymer-BPA was taken up into cells by endocytosis through LAT-1 transporter and remained in the endosome. Taken together, PEG-PLys(-fructose)-BPA should be internalized into the cancer cells via LAT-1 mediated endocytosis.
In in vivo study, PEG-PLys(fructose)-BPA showed drastically higher tumor accumulation than conventional fructose-BPA complexes and maintained high boron concentration for 6 h. Ultimately, in the study of tumor suppression, 18 days after thermal neutron irradiation, PEG-PLys(fructose)-BPA significantly suppressed the tumor growth without apparent side effects compared to the fructose-BPA complexes.

Conclusion
PEG-PLys(fructose)-BPA exhibited high accumulation and prolonged retention within the tumor, and exerted significantly enhanced BNCT effect compared with the conventional fructose-BPA complexes. PEG-PLys(fructose)-BPA has a great potential for clinical use in BNCT..

Keyword: BPA, fructose, functional polymer, LAT1, endocytosis

Pa P1 01

Accelerator Neutron Source for in-vitro and in-vivo BNCT studies

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Introduction
A source of epithermal neutrons based on vacuum-insulated tandem accelerator and a lithium target was proposed and developed for the technique of boron neutron capture therapy. A stationary proton beam of 2 MeV with a current of up to 6 mA was obtained in the accelerator. Neutron generation was performed and the flux and neutron spectrum were experimentally measured.

Materials and Methods
The work was carried out on an accelerating neutron source created at the Budker Institute of Nuclear Physics. The accelerator was equipped with wire scanner OWS-30 (D-Pace), non-contact current sensor Bergoz, infrared camera FLIR, pyrometer, cooled diaphragms to ensure long-term stable operation. The source of neutrons provides the epithermal neutron flux density to 3 108 cm-2 s-1. The test cell cultures or mice are placed inside a plexiglas phantom mounted on a rotating table. The neutron flux is monitored by a neutron detector based on the GS20 scintillator (Saint-Gobain Crystals) and a set of activation foils SWX-1552 (Shieldwerx). The total neutron yield is measured by target activation with beryllium-7. The absorbed dose is determined by performing numerical calculations of neutron transport and gamma radiation by the Monte Carlo method. For carrying out biological studies, the unit is equipped with an atomic emission spectrometer ICPE-9820 (Shimadzu) and other necessary equipment.

Results
The effect of a space charge and aberrations of a focusing magnetic lens on a beam of negative hydrogen ions injected into accelerator was discovered. Taking into account, this effect and visualization of the ion beam made it possible to ensure a stable long-term operation of the accelerator with high current. The x-ray and gamma-radiation dose rates and spectra and the neutron-emission dose rate upon the absorption of 2-MeV protons in various materials have been measured along with the residual-activity radiation spectrum. In situ observation of blistering of samples prepared from copper and tantalum was performed during their irradiation with a 2-MeV proton beam. The results of these studies determined the design of the neutron-generating target. A series of biological studies were carried out together with a number of Russian and Japanese scientific organizations. It was established that neutron irradiation of tumor cells, previously incubated in a medium with boron, led to a significant suppression of their viability. Irradiation of mice with

grafted human glioblastoma tumor led to their complete cure. A new method for measuring the absorbed dose based on the activation of stable nuclei introduced into the composition of the targeted delivery of boron is proposed and tested. A beam shaping assembly was developed and manufactured, which makes it possible to form a therapeutic beam of neutrons at 2.3 MeV proton energy to the greatest extent satisfying the requirements of BNCT.

Conclusion

The accelerator neutron source created at the Budker Institute of Nuclear Physics provides a beam of epithermal neutrons and provides an opportunity to conduct research in the field of BNCT. The results of biological studies have confirmed the acceptable quality of the neutron beam. At present, the neutron source is being modernized to produce a therapeutic neutron beam to the greatest extent satisfying the requirements of BNCT.

Keyword: accelerator, lithium target, epithermal neutrons

Pa P1 02

In Situ Observations of Blistering of a Metal Irradiated with 2-MeV Protons

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Introduction

In accelerator neutron sources for BNCT, neutron generation is performed by dumping a proton beam onto a target. In most cases the target is a thin layer of lithium or beryllium deposited on the structural metal. With irradiation of the target by protons, deformation of the surface layer occurs in the form of numerous blisters, which leads to a decrease in thermal conductivity and limits the time of operation. Experimental data on the critical dose of blistering have been extremely scarce and are absent for a proton energy of about 2 MeV. The aim of this study was to investigate the blistering, under 2-MeV proton irradiation, of samples made of copper, beryllium, tantalum and copper-tantalum alloys.

Materials and Methods

A vacuum-insulated tandem accelerator was used to observe in situ blistering during 2-MeV proton irradiation of metallic samples. Samples consisting of copper of different purity, beryllium, tantalum, and tantalum-copper compounds were placed on the proton beam path and forced to cool. The surface state of the samples was observed using a CCD camera with a remote microscope. Thermistors, a pyrometer, and an infrared camera were applied to measure the temperature of the samples during irradiation. After irradiation, the samples were analyzed on an X-ray diffractometer, laser and electron microscopes.

Results and Conclusion

The key results of the performed studies on 2-MeV proton irradiation of different samples as follows:

The blistering threshold of the copper surface depends on the copper purity. The purer the copper, the higher the threshold is. The maximum threshold is 3 10**19 cm**-2; the minimum value is seven times lower.

Once blisters appear on the copper surface, further irradiation does not cause any more surface modification, which can be due to the formation of holes and cracks when blisters emerge.

The attachment of a thin tantalum foil to copper by explosion or diffusion welding as well as soldering is resistant to a heat load of up to 1 kW/cm**2.

Tantalum is much more resistant to the formation of blisters than copper. The threshold of blisters in the form of bubbles or flakes on the tantalum surface exceeds 6.7 10**20 cm**-2. At fluence of 3.6 10**20 cm**-2 the surface is modified in the form of a relief with a characteristic cell size of 1 micron.

During tantalum irradiation, an increase in the sample surface temperature was detected. This could be due to a decrease in the thermal conductivity because of the appearance of cavities and hydrogen incorporation into the tantalum crystal structure.

In relation to the problem of developing target for the accelerator-based epithermal neutron source for BNCT the results mean the following:

Ultra-pure copper can be used to prepare a substrate for the target in the therapy of several patients (approximately 20).

It is not obvious that after the appearance of blisters on the surface of the copper substrate the target cannot continue to be used to generate neutrons. This is because accumulated hydrogen can escape through holes and cracks formed when blisters emerge. Further-

more, a decrease in the thermal conductivity caused by blisters will not be critical for lithium melting.
The application of a thin tantalum layer deposited on the heat-removing copper substrate increases the target resistance to blistering by no less than ten times as compared to the most stable copper substrate.
Proton absorption in the tantalum layer of the target decreases the thermal conductivity due to the formation of cavities and hydrogen incorporation into the tantalum crystal structure, and consequently, leads to a significant increase in the lithium temperature, which can be critical even without surface modification by blisters.

Keyword: blistering, proton, neutron producing target

Pa P1 03

A real-time neutron monitor for BNCT

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Introduction:
Real-time measurement of thermal neutron flux is desirable to further improve the safety and precision of BNCT. Currently, neutron flux is estimated using the Au radio-activation method. With this method, the flux can be obtained only after a certain period of time. To advance BNCT, we are developing a real-time neutron monitor. The detector in this system consists of a small grain scintillator, an optical quartz fiber, and a photo-multiplier tube. The scintillator is a LiCaAlF6 (Eu doped) crystal whose scintillation decay time is 1.6 μs. Thanks to the tiny crystal mounted at the small detector head, this detector is capable of discriminating neutrons from gamma rays without significantly perturbing the neutron field. In this work, we evaluated the monitor's dynamic range to check whether it can be applied to a BNCT neutron field, which is on the order of 10^9 n/cm^2/s.

Materials and Methods:
Neutron counts were measured with our neutron monitor at several thermal flux between 2×10^7 n/cm^2/s and 2.2×10^9 n/cm^2/s. Thermal neutron fields were produced by the Neutron exposure Accelerator System for Biological Effect Experiments (NASBEE) at the National Institute of Radiological Sciences. The flux was estimated by activating a gold foil with and without a Cd filter and measuring its activity. Absolute thermal flux was obtained with the cadmium difference method. Two detectors were exposed to the same field simultaneously and neutron counts were calculated with our pulse height distribution analysis software.

Results:
Plots of neutron counts against thermal neutron flux for both detectors show good linearity over the measured flux range.

Conclusion:
In current accelerator-based BNCT, approximately 2×10^9 n/cm^2/s neutron flux can be expected. Our neutron monitor shows good linearity at least up to 2.2×10^9 n/cm^2/s. Hence, it can be utilized to measure BNCT neutron fields. We envisage that this monitor will be applied to checking beam output constancy before treatment delivery and monitoring beam stability and output during treatment.

Keywords: Real-time neutron detector, Scintillator with optical fiber, Beam QA

Pa P1 04

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

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Introduction:
The interest of BNCT in Korea has been increased gradually as the number of cancer patients has been increased. An accelerator based BNCT(A-BNCT) system is under development with a goal to use practical cancer treatments within about 1 hour therapeutic time for a hospital based facility in Korea.

Material and methods:
To meet the goal we have designed and developed a high power accelerator, a beam delivery system and its target moderator assembly to produce a high epithermal neutron

flux of 2x109 n/cm2•s. It consists of a 10MeV proton linear accelerator and a high power beryllium target system and a moderator-collimator system under the consideration to reduce residual gamma radiations and fast neutrons.

Results:
A-BNCT has a capability of production of higher epithermal neutron flux and lower residual radiation doses than the IAEA BNCT recommendation. This paper focused on the some details of performance verification about the proton accelerator and the neutron generator system in a practical epithermal neutron source for hospital-based uses.

Conclusions:
A-BNCT system within about 1 hour therapeutic time in Korea has been developed as scheduled. And this hospital based BNCT system will be convenient and useful for cancer patients.

Keyword: accelerator, A-BNCT system

Pa P1 05

Development and experimental verification of a liquid moderator based neutron spectrometer

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Introduction
Recently, accelerator-based neutron sources (ABNS) are being developed for BNCT instead of nuclear reactors. Generally, the neutron energy spectrum in the irradiation field formed by an ABNS is strongly dependent on the design of the ABNS, e.g., the type of target nuclide, type of bombarded particle, and structure of its beam shaping assembly. Therefore, it is very important to measure the neutron spectrum in the treatment room to determine the patient dose correctly since the dose is highly depending on the neutron energy spectrum. To solve this issue, we have been developing a new neutron spectrometer for a wide dynamic energy range, from thermal to fast neutron energy regions, especially for epithermal neutron mainly used in BNCT. In this study, we developed a real liquid moderator based neutron spectrometer, and performed some experiments to verify the performance of this device.

Materials and Methods
Experiments were performed at Facility of Radiation Standards (FRS) in Japanese Atomic Energy Agency (JAEA). We performed two kinds of experiments. At first, we performed the mono-energetic neutron measurement to examine the accuracy of the evaluated response function of the developed spectrometer, calculated by MCNP-5. The neutron energies measured in this experiment were 525 keV, 250 keV and 144 keV. Measured values were compared with the both evaluated response function and simulated values calculated with MCNP-5. Secondary, we measured a neutron field generated by Cf-252, because the neutron spectrum emitted by Cf-252 was well known and it enables us to examine the performance of the developed spectrometer by measuring that spectrum. The measured result of Cf-252 irradiation were also compared with simulated values, and a neutron spectrum was evaluated by unfolding the measured data.

Results
As a result of the mono-energetic neutron measurement, we confirmed that the evaluated response function was systematically over estimated, multiplied by roughly a factor of 2, even though the .simulated values were well agreed with the experimental values. In Cf-252 neutron measurement, we confirm that the measured data and simulated detector signal counts were well agreed, and the evaluated neutron spectrum was also well agreed with the theoretical neutron spectrum emitted from Cf-252.

Conclusion
In this study, we developed a liquid moderator based neutron spectrometer, and performed two kinds of experiments to confirm the performance of the developed spectrometer. As a result, we confirmed that this developed spectrometer has very good performance. In future, we will measure other neutron energy spectrum, for example, other energies of mono-energetic neutron, thermal neutron field, complex white spectrum, and especially epithermal neutron field that is important for BNCT Acknowledgments We thank all personnel at FRS, JAEA, for their contribution to our experiments, especially for Yoshihiko Tanimura and Sho Nishino. This work was supported by JSPS KAKENHI Grant-in-Aid for JSPS Fellows Number 16J000930.

Keyword: neutron detector, neutron spectrometry, unfolding, mono-energetic neutron, Cf-252

Pa P1 06

Monte Carlo Simulation and Experimental Characterization of Tissue Equivalent Proportional Counter (TEPC) for Neutron Dosimetry

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Introduction

A Tissue Equivalent Proportional Counter (TEPC) is the radiation detector used for experimental microdosimetry. The TEPC offers a physical approach of measuring energy depositions in microscopic volumes by filling the gas cavity with low pressure gas. It has also been widely used for dosimetry in mixed radiation fields such as the space radiation environment and boron neutron capture therapy (BNCT) due to its ability to separate contributions from different types of radiation. In this study, Monte Carlo (MC) modelling and experimental measurements of the response of a novel TEPC to a neutron source was conducted.

Materials and Methods

The spherical TEPC designed and developed by the Korea Astronomy and Space Science Institute (KASI) was implemented in this study. The sensitive volume of the TEPC was 60 mm in diameter and was filled with pure propane gas at a pressure of 13.9 Torr to simulate a 2 um diameter site. The gas cavity is surrounded by a 3 mm thick A150 tissue equivalent (TE) plastic and was housed in 1.5 mm thick aluminum. To study the response of the TEPC to a mixed radiation field, the TEPC was exposed to a Californium-252 neutron source (Eckert and Zeigler, Germany) positioned 1 m away and the pulse height spectrum was recorded with a lower detection threshold of 0.2793 keV/um. Identical set-up was implemented for the Monte Carlo modelling of the TEPC which was performed using Geant4 toolkit version 10.03.p01. The Lawrence Livermore National Laboratory (LLNL) Fission Model was used to model the Cf-252 source. The event-by-event energy deposition in the gas cavity was scored and was divided by the mean chord length (i.e., 1.33 um for a 2 um site) to obtain the lineal energy (y). An in-house MATLAB code was created to construct the frequency- and dose-weighted lineal energy spectrum (i.e., yf(y) and yd(y) spectrum, respectively) and to calculate microdosimetric quantities for both experimental and simulation results.

Results

The yf(y) and yd(y) spectra for both experimental and simulation results were constructed and compared. Three prominent peaks can be observed from yd(y) spectra. The first, second and third peaks occurred at $y < 10$ keV/um, 10 keV/um $< y <$ 100 keV/um and $y >$ 100 keV/um, respectively. As shown in the simulation results, these peaks corresponded to depositions due to electrons from gamma interactions (1st), recoil protons from neutron interactions (2nd) and contributions from interactions other than the previously mentioned ones (3rd). The frequency mean lineal energy (yF) and the dose mean lineal energy (yD) were also calculated for both the experiment and simulation. The yF for the experimental and simulation results were 12.8 keV/um and 9.0 keV/um, respectively. This resulted in a 30% difference which can be attributed to the detection limitations of the TEPC. The microdosimetric quantity of greater importance is the yD which indicates the average lineal energy that contributed to the dose. The experimental and simulated yD were 53.0 keV/um and 55.4 keV/um, respectively. Only a 4.5% difference was observed for the experiment and simulation because low lineal energy depositions contributed little to the dose. Despite the slight difference at low y values in yd(y) spectrum, the results showed a good agreement between the experimental and simulated results.

Conclusions

Experimental measurements to observe the response of the TEPC was conducted and was validated using MC simulations. The results of this study indicate the potential of TEPC in mixed field dosimetry and can be valuable in designing mini-TEPCs suitable for BNCT dosimetry.

Keyword: tissue equivalent proportional counter, neutron dosimetry, lineal energy, Monte Carlo simulation

Pa P1 07

Study of the role of neutron induced nuclear reactions on chlorine in healthy tissue dosimetric calculations for BNCT. Measurement of their cross sections at n_TOF (CERN).

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Introduction:
Chlorine is present in the human body in low concentration, this concentration reaches a maximum in the brain, with 0.3 % of the mass. As it is well known, one of the most important applications of BNCT is the treatment of glioblastoma multiforme. There are nuclear reactions that neutrons used in BNCT can induce in the brain chlorine, releasing heavy charged particles (protons) or gamma rays. The energy deposited by these particles in healthy tissue might have an important impact in the delivered dose.

Materials and Methods:
We have performed Monte Carlo simulations to estimate the impact of the 35Cl(n, p)35S and 35C(n, g)36Cl reactions on the released energy in brain healthy tissue. As output of this simulation study we came to the conclusion that a better knowledge of the cross section of the mentioned reactions is necessary in order to estimate their contribution below 5 % of uncertainty. To do so, two proposals of experiment were presented to the INTC committee of CERN for the measurement at n_TOF (neutron time of flight facility at CERN) of the cross section of these reactions. Both of them were approved. The experiment for the measurement of the 35Cl(n, p)35S cross section was carried out in October 2017 and the one for 35Cl(n, g)36Cl is scheduled for summer 2018.

Results:
From the Monte Carlo simulations, we obtained that the contribution of the reactions induced in chlorine is not negligible for precise treatment plannings. Pursuing an integral and accurate comprehension of the involved processes and their importance we are carrying out the experimental work and the data analysis of the measurements. In this talk we will explain the performed simulations and their results, as well as the status of the experimental work and its preliminary results.

Conclusion:
Boosting our knowledge on the nuclear processes involved in BNCT treatments we will be able to better adjust the delivered dose in the different types of tissue and, therefore, design more effective plannings. In this context, our work is focused on the chlorine impact, that seems to be much higher than expected.

Keyword: Chlorine, glioblastoma, n_TOF, Monte Carlo

Pa P1 08

Evaluation of silicon based microdosimetry for boron neutron capture therapy Quality Assurance using fast neutron beams

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Introduction:
The shift from reactor to accelerator based neutron production has created a renewed interest in Boron Neutron Capture Therapy (BNCT). BNCT is reliant upon the favourable uptake of Boron-10 by tumour cells and their interaction with neutrons to produce high LET fragments (He-4 and Li-7 nuclei) that deposit energy locally within the tumour cells. As with any radiation based treatment, Quality Assurance (QA) is crucial. The dose enhancement of BNCT in fast neutron therapy (FNT) was investigated. Experimental and simulation results are compared using the latest generation Silicon on Insulator (SOI) microdosimeters from the Centre for Medical Radiation Physics (CMRP).

Materials and Methods:
Monte Carlo calculations were used to characterize the fast neutron source produced at the National Accelerator Centre (NAC) iThemba LABS in South Africa. High energy neutrons are produced by the reaction of 66-MeV protons on a Be target. Geant4 version 10.01 was used to model the entire beamline, including target system and beam-shaping assembly (BSA). The phase space of the beam at isocentre was used to simulate a typical clinical treatment. Experimental measurements were taken at the facility using the MicroPlus probe connected to Bridge SOI microdosimeter. Different neutron conversion materials were investigated such as enriched Boron-10 carbide, which were sourced from the European Spallation Source (ESS).

Results:
The measured neutron spectra produced at the NAC facility agrees well with that calculated using the Monte Carlo simulation codes. The epithermal component (< 10 keV) calculated using Geant4 is slightly higher compared to published results using MCNP4

(Bohm 1999) due to the difference in physics models. The microdosimetric response obtained experimentally is validated by simulation results. This allows the different dose components to be distinguished such as alpha and lithium nuclei from BNC and low energy proton recoils from fast neutron scatter. Different Geant4 physics libraries were compared with reference to experimental results in order to produce a simulation application suitable for fast neutron therapy. During irradiation, the Bridge microdosimeter presented a low activation and fragmentation rate of secondary particles. As seen in other treatment types such as carbon ion therapy, the SOI demonstrates a high level of radiation hardness.

Conclusion:
The suitability of a Geant4 simulation for modelling BNCT in fast neutron therapy has been shown. The simulation application was developed, incorporating all technical information of the beamline provided by the NAC. The results indicate that the Bridge SOI microdosimeter is particularly useful for fast neutron therapy microdosimetry due to its radiation hardness and low activation rate. Additional Monte Carlo simulation codes such as MCNP6.2 have been investigated in the same context. Full results and details will be presented in a final paper.

Keyword: BNCT, microdosimetry, FNT, Geant4, MCNP

Pa P1 09

Uncertainties in the absorbed dose determination in irradiations with epithermal neutrons due to the dependence of neutron transport on shape and size of the exposed volume

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Introduction: The evaluation of the absorbed dose in BNCT treatments performed with epithermal neutrons, as required for deep tumors, is a challenging task. A peculiarity that causes uncertainties of dose determinations is given by the dependence of the thermal neutron fluence ϕth on the size and shape of the irradiated volume and also on the direction of incidence of the beam. Consequently, the therapeutic dose DB, deriving from 10B reactions with thermal neutrons (10B(nth, α)7Li), and the gamma dose Dγ, mainly coming from reactions of thermal neutrons with hydrogen (1H(nth, γ)2H), also depend on the shape and size of the irradiated volume. The dose due to fast-neutron collisions (Dfast), unlike DB and Dγ, is not greatly dependent on the geometry of the irradiated volume, except in the peripheral regions.
Owing to the short range of the α and7Li charged particles, the therapeutic dose DB is proportional to ϕth and can be evaluated, in each position, by means of the neutron kerma factor, if both ϕth and the 10B concentration, in that position, are known. On the opposite, owing to the long range in tissue of the photons of 2.2 MeV emitted in the reactions of thermal neutrons with hydrogen, Dγ has a spatial distribution different from that of ϕth and undergoes changes greater than those of DB by changing shape or size of the irradiated volume.

Materials and Methods: Monte Carlo (MC) simulations and experimental measurements in water phantoms have been carried out. The considered epithermal neutron beam was that of the LVR-15 research reactor, designed and exploited for BNCT at the Research Centre Řež. MC calculations have been performed by means of MCNP/MCNPX. Measurements of neutron fluences and absorbed doses were performed with Fricke-gel dosimeters, thermoluminescence detectors and activation foils.

Results: The following data have been attained: (i) variation of neutron spectrum versus depth in water, (ii) thermal and epithermal neutron fluence profiles in phantoms with different shape or size and different direction of incidence of the beam and (iii) Dγ profiles in the various phantoms. Information as a function of both the depth in phantom and the distance from the beam axis has been achieved. The calculated and experimental outcomes were consistent. The results obtained with different phantoms have shown significant dependence of ϕth and Dγ on the phantom geometry.
Also a few evaluations of ϕth and Dγ in phantom containing 157Gd have been done. Owing to the high cross section of the reaction 157Gd(nth, γ)158Gd, both ϕth and Dγ can be significantly affected by the presence of 157Gd.

Conclusions: The results of the work have given useful information that allows a first estimate of the extent of the inaccuracy that may result from imprecise geometry settings in treatment planning.

Keyword: Neutron spectrum vs depth, Dose dependence on irradiation geometry, Effects on dose of 157Gd

Parallel Session

Pa P1 10

COMMISSIONING OF THE NUBEAM BNCT NEUTRON SOURCE AT HELSINKI UNIVERSITY HOSPITAL CANCER CENTER

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Helsinki University Hospital (HUH) and Neutron Therapeutics (NT) have a joint project to install a nuBeam suite for boron-neutron capture therapy (BNCT) in the HUH Cancer Center. nuBeam is a compact accelerator based neutron source which can be installed in a hospital environment. The safety and efficacy of the biologically targeted form of radiation therapy of the L-BPA-F mediated BNCT, have previously been evaluated in the clinical protocols of head and neck carcinomas and malignant gliomas using the epithermal neutron beam at the Finnish research reactor FiR 1 as the neutron source.

The lack of neutron sources suitable for hospital environment has limited the adoption of BNCT. NT's nuBeam suite is the first accelerator-based neutron source of its kind to operate in the world. nuBeam has a unique electrostatic accelerator design and a proprietary rotating solid lithium target technology, which results in a system with high reliability.

Helsinki University Hospital is building a new radiation therapy facility for BNCT treatments inside the hospital area. The facility consists of an accelerator room, treatment room, control room, patient preparation room, boron laboratory and dosimetry rooms. For radiation safety reasons, the accelerator and treatment rooms are built with heavy concrete. In addition, the treatment room walls, doors and floor are covered with lithium plastic to slow down and absorb the neutrons. Doors are shielded with lead, and equipped with "last-man-out" sweep switches. The treatment room will be equipped with a patient positioning system and a CT for image-guided BNCT treatment.

The project aims at a clinically functional BNCT treatment. The starting point and the goal are based on the experience accumulated during the Finnish research reactor-based BNCT project. The current project has three phases: the installation and testing of the neutron accelerator (step 1), early clinical BNCT use with ethically approved clinical protocol (step 2), and established use of BNCT through clinical protocols (step 3).

This presentation focuses in the first step of the project, where the accelerator is installed and the radiation safety of the facility is confirmed. After the neutron source is functional, the neutron beam will be characterized and the BNCT dose planning system will be verified. In the end of step 1, the patient safety of the BNCT system required for clinical use is confirmed, and early clinical BNCT of the facility can start.

Keyword: BNCT, Accelerator, Neutron source, Facility

Pa P2 01

Beam characteristics and in phantom dosimetry for accelerator-based boron neutron capture therapy: Comparative study of Monte Carlo simulations using Geant4 and MCNP6

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Introduction

An accelerator-based boron neutron capture therapy (A-BNCT) facility is under construction in Korea for an epithermal neutron source.

In this study, neutron beam characteristics and therapeutic dose calculations of the A-BNCT facility were carried out by using Monte Carlo simulations.

Materials and Methods

1. Target and moderator design

The Pohang Accelerator Laboratory (PAL) designed and revised the target and moderator assembly of the facility. The target was composed of beryllium and copper. The copper was used as a supporting material to exchange heat due to its high thermal conductivity.

2. Monte Carlo Simulations

Geant4 version 10.3 and MCNP6.1 were used for comparative study of neutron beam characteristics and in phantom dose caclulations. The physics model for the Geant4 is "QGSP_BIC_AllHP" with TENDL-2014 and ENDF/B-VII.1 nuclear data library. MCNP6.1 simulation were conducted with "Bertini" physics model and nuclear data evaluation ENDF/B-VII.1.

It was assumed that a 10 MeV incident proton beam hits the beryllium target with a uniform square field (13 x 13 cm2) and produce a neutron source. The phase-space file containing position, direction, energy, and particle type information, was made at the end of

the moderator. This phase space file was used to irradiate on the CT images of a brain.
3. A-BNCT dosimetry
A spherical tumor, 4 cm in diameter, was located in patient's DICOM CT images in 5 cm depth. The boron concentration was assumed to be 15 and 60 ppm in the normal tissues and tumor, respectively. The A-BNCT dose has four components, 1)boron dose from alpha and 7Li particles, 2)nitrogen dose, 3)fast neutron dose and 4)gamma dose. The reaction of each component was classified and recorded by Monte Carlo simulations. The weight factors CBE (Compound Biological Effectiveness) and RBE (Relative Biological Effectiveness) were also considered. The values of CBE for the boron dose and RBE for the others were taken from the previous study.

Results
1.Beam characteristics
Epithermal neutrons are more than 85% of all at the exit of the beam. There is a peak between 300 to 400 keV in gamma spectrum caused by nuclear reaction of neutron with boron in moderator. The total neutron and gamma fluence are two to three times higher in MNCP6.1 than in Geant4. Though the energy spectrum is similar in MCNP6.1 and Geant4 results.
2. Dose along the beam center line
The boron dose increased steeply in tumor region which verifying a therapeutic effect. However, the fast neutron and gamma contributed to most of the dose at the shallow depth. This problem can be arranged by modifying moderator and collimator design.

Conclusion
The beam characteristics and doses in CT images were successfully calculated by using Monte Carlo simulations. However, there were some differences in total fluence between MCNP6.1 and Geant4 results, as well as gamma and fast neutron dose dominating in the shallow depth. A further investigation to address such differences are undertaken to date. The data will be utilized in treatment planning system and clinical research area.

Keyword: A-BNCT, Monte Carlo simulation, dose calculation, beam characteristics, treatment planning system

Pa P2 02

Development status of BNCT Treatment Planning System: SACRA planning

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In recent years, accelerator-based BNCT system have been actively developed all over the world. We have developed a Cyclotron-based BNCT system and are currently conducting clinical trials in Japan. As in general radiation therapy, dose evaluation must be performed prior to treatment using a treatment planning system (TPS). Several BNCT TPS's were developed for clinical trials using reactors, but most of these projects have since come to a halt. Regulations on medical device software differ across countries, but a TPS with medical device approval is necessary for widespread adoption of BNCT. Therefore, we are developing a treatment planning system for accelerator-based BNCT called SACRA planning.
SACRA planning implements Monte Carlo dose calculation based on PHITS, and it is capable of dose calculation and evaluation for CT, MRI and PET images, similarly to general radiation therapy software. In this presentation, we will introduce the development status of SACRA planning.

Keyword: SACRA planning, Treatment Planning System, TPS, Monte Carlo, PHITS

Pa P2 03

Neutron beam quality measurement of accelerator-based neutron source using microdosimetric technique

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Introduction
An accelerator-based neutron source is gaining interest due to its ability to perform treatments, such as BNCT in a hospital environment. Currently, many facilities are trialling accelerator based BNCT. The accelerator-based neutron source at Aomori prefecture Quantum Science Center (QSC) is primarily used for cell and small animal studies. In

a typical BNCT field, there exists many different types of radiation with each having a different biological effect. To maximise the treatment efficiency, it is important to understand the beam quality of the neutron source. Microdosimetry is a technique used to measure radiation in a mixed field. Using this technique, it is possible to derive the relative contributions of each radiation component. A tissue equivalent proportional counter (TEPC) measures energy deposition in a simulated micrometer scale volume comparable to that of a living cell. The TEPC uses material and gases that are essentially equivalent to human tissue in chemical composition. This study presents the microdosimetric spectrum of the accelerator-based neutron source at QSC.

Material and method

The accelerator-based neutron source at QSC consists of a 20 MeV proton beam and a beryllium target. A moderator system was designed to slow down the fast neutron component to increase the thermal neutron flux. The microdosimetric spectrum was measured using the Far West Technology Inc. LET 0.5 inch TEPC. The counter was filled with a methane-based tissue equivalent gas at a pressure of 74.5 hPa to simulate a 1 μm diameter sphere. Microdosimetric single event spectra was calculated using the Particle and Heavy Ion Transport code System (PHITS) version 2.88. The specific energy distribution (T-SED) tally was used to calculate the probability density of deposition energies inside the TEPC. The obtained results were compared to the microdosimetric spectrum of the Kyoto University Reactor (KUR) mixed irradiation mode, which is also used for animal studies.

Results

The microdosimetric spectrum was calculated using PHITS and the electron and proton edges, 15 keV/μm and 100 keV/μm, respectively, were clearly visible. Compared to KUR, the accelerator-based neutron source has a higher flux of fast neutrons, which resulted in a higher production of recoil heavy nuclei. The relative contribution from protons, carbon ions and alpha particles were approximately 0.8, 0.15 and 0.02, respectively, for the accelerator-based and 0.88, 0.08 and 0.03 for KUR.

Conclusion

The microdosimetric spectrum of the QSC accelerator-based neutron source was successfully calculated using PHITS. The relative contributions from protons, carbon ions and alpha particles were approximately 0.8, 0.15 and 0.02 respectively. Experiments will be performed to validate the simulation results.

Keyword: Microdosimetry, Accelerator-based BNCT, TEPC, Monte Carlo simulation

Pa P2 04

Characterization Study of Boron-10 Doped Nanodiamonds Made by Ion Implantation

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Introduction

Nanodiamonds (NDs) have been proved to have good biocompatibility from many previous studies. In this work, we present a physical method to prepare boron-10 contained nanodiamonds (BNDs) by boron-10 ion implantation to embed boron-10 atom into NDs. The follow on studies of this BNDs, such as physical properties, were investigated in this work. It is our ultima goal to prove such boron-10 embedded NDs can be effectively used as a boron-10 carrier without cytotoxicity for BNCT purpose.

Materials and Methods

NDs powder was applied to silicon wafer and form a very thin layer of NDs on the wafer surface. The wafer was then implanted with boron-10 with energy between 20-80 keV with total dose > 5x1015 ions/cm2. The adhesive between ND and wafer is water soluble, so that the boron-10 implanted NDs can be reclaimed using an ultrasonic basin. Transmission electron microscopy(TEM), Raman spectrum, photoluminescence (PL) spectrum were used to analyze the samples' properties.

Results

The boron-10 atoms are successfully embedded into NDs through straightforward ion implantation process. No chemical reactions are required during all processes. The implant damages to NDs is repaired by an annealing process, which recovers NDs crystal structure. The results of TEM and Raman examinations indicate the crystal structure of the BNDs recovered completely by thermal annealing. Meanwhile, the PL measurement results indicate the florescence of BNDs is enhanced due to the vacancies creation by the ion implantation process. The enhanced florescence property can be used to observe the intracellular distribution of BNDs. All measurement results show boron-10 implanted NDs have preserved the properties of non-implanted NDs.

Conclusion
The NDs has unique feature of its surface functionality, which enables DNs to be utilized as targeting agent through medical synthesis. In this study, we show the boron-10 embedded BNDs through ion implantation can maintain surface functional properties of NDs. Therefore, BNDs, as a boron -10 carrier, can be used to form various targeting agents and be delivered to specific locations for BNCT cancer treatment.
Acknowledgements We thank Dr. Causon K.C. Jen at Axcelis Technologies, Inc. for his valuable inputs.

Keyword: nanodiamond, boron ion implantation, TEM, PL

Pa P2 05

A New Boron Delivery Agent: Boron-10 Doped Nanodiamonds Made by Ion Implantation

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Introduction
Boron Neutron Capture Therapy (BNCT) has been demonstrated as an alternative to conventional radiation therapy for the treatment of different cancers. One of the critical parts of BNCT is boron delivery agent. Nanodiamonds (NDs) have been proved to have good biocompatibility from many previous studies. In this work, we introduce boron-10 implanted nanodiamonds (BNDs) as a new boron delivery agent with good biocompatibility for the first time. The cytotoxicity study of BNDs and simple targeting demonstration using BNDs were incorporated in this work.

Materials and Methods
NDs powder was applied to silicon wafer and form a very thin layer of NDs on the wafer surface. The wafer was then implanted with boron-10 with energy between 20-80 keV with total dose > 5x1015 ions/cm2. The adhesive between ND and wafer is water soluble, so that the boron-10 implanted NDs can be reclaimed using an ultrasonic basin. The cytotoxicity was measured by MTT assay. Fluorescence microscopy was used to observe the BNDs intracellular distribution inside HeLa cells with and without transferrin coating.

Results
First, the cytotoxicity of BNDs is evaluated for potential bio-applications. The MTT assay results indicate BNDs is non-toxic, which is well expected because of the boron-10 is embedded inside the NDs and the nanodiamond original properties are preserved. The stability of the boron atoms inside the NDs guarantees a safe and extended usage of such nanoparticles. To perform effective BNCT, one needs to increase the tumor uptake of boron-10 concentration from delivery agent. A simple targeting using BNDs is demonstrated here. By surface coating transferrin, we observe that the cellular uptake of the BNDs is increased. The high uptake efficiency for BNDs together with its non-cytotoxicity can pave the way for its use in BNCT for effective cancer treatment.

Conclusion
The BNDs keep the same properties of NDs which is non-cytotoxicity and biocompatible. Because of these important properties, the dosage of BNDs can be increased to achieve better treatment efficiency. Moreover, higher tumor uptake than normal tissue can be achieved through surface modification of BNDs with effective targeting agent. All existing problems of boron delivery agent for BNCT can be potentially solved. It makes the BNDs become a new venue or hope of BNCT and therefore is worth of continue investigation.
Acknowledgements We thank Dr. Causon K.C. Jen at Axcelis Technologies, Inc. for his valuable inputs.

Keyword: nanodiamonds, boron ion implantation, BNCT, MTT

Pa P2 06

BNCT RESEARCH FACILITY AT MARIA REACTOR (NCBJ, POLAND) – NUMERICAL MODELS AND FIRST MEASUREMENTS

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Introduction
In the National Centre for Nuclear Research (NCBJ) in Poland the H2 facility for BNCT research is being constructed as a part of a new laboratory at one of the horizontal channels of MARIA reactor. In order to obtain a neutron beam, an intermediate channel, in the form of a tube between the reactor vessel and the channel stub pipe, has to be mounted in the reactor pool. Since the MARIA reactor is one of the world biggest producers of molybdenum for nuclear medicine, the essential condition for the BNCT beam design is not to interfere with regular operation of the reactor. In particular, there is no possibility to switch off the reactor in order to provide safe access for the researchers to the irradiation room. Therefore a beam shutter was designed, based on numerous numerical models performed with MCNP6 code.

Materials and Methods
The intermediate channel will be mounted by the end of April 2018. Filling its tube with gas (nitrogen) will open a duct in the biological barrier, which is the water filling the reactor pool, leading the beam out for irradiation. Releasing the gas will close the duct again. Together with the beam shutter it will allow for entering the room during reactor operation. According to the Monte Carlo modelling of the reactor, performed with MCNP6 code, the neutron spectrum of the beam obtained will have its maximum at thermal energies, therefore, it will allow for experiments with cellular samples and small animals. As a second step, a neutron converter, a subcritical system to shift the energy spectrum to the higher energies (in fission reaction of U-235), will be located in the periphery of the reactor core, in front of the intermediate channel, providing a fast neutron beam. Hence, a significant quantity of heat is generated in the fission reaction, a proper cooling conditions must be provided. Thermo-hydraulic conditions inside the uranium converter were studied thoroughly using CFD code (ANSYS Fluent 17.2), heat fluxes were obtained with MNCP6 code and further applied to Fluent. Installation of the converter is planned for the first quarter of 2019, meanwhile tests with a converter mock-up are in preparation. The beam shape assembly mounted inside the horizontal channel will allow for slowing fast neutrons down to epithermal energies.

Results
The first version of the BSA for H2 channel of MARIA reactor was designed several years ago. Recently the changes and improvements of the design are being made and modelled using MCNP6 code. The models included the reactor core calculations, the neutron transport through the channel, and the radiation conditions in the irradiation room with the beam shutter implemented. Its unique design allows setting it in four different positions, for shutting the beam or for choosing one of three sets of filters/moderators for shaping the beam.

Conclusions
The measurements to verify the numerical modelling of the radiation conditions in the room with opened intermediate channel are planned for July 2018. The results will allow to ultimately confirm the parameters of the shutter before its implementation.

Keyword: reactor beam, shielding, converter, Monte Carlo

Pa P2 07

Verification for dose estimation performance of a Monte-Carlo based treatment planning system in University of Tsukuba

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[Introduction] A project team (iBNCT) with University of Tsukuba is developing a linac-based neutron source for boron neutron capture therapy (BNCT). The team plans to carry out a clinical study using the device without delay. In the iBNCT project, we are developing not only the neutron source device but also several peripheral devices needed in BNCT treatment [1]. As a part of the development, a multi-modal Monte-Carlo based treatment planning system (Developing code: Tsukuba-Plan) is being produced. The Tsukuba-Plan has employed PHITS as Monte-Carlo dose calculation engine. To apply the Tsukuba-Plan to actual BNCT treatment, we are currently performing several verifications.

[Materials and methods] To verify dose estimation accuracy of the Tsukuba-Plan, calculation values determined from the Tsukuba-Plan were compared with experimental values. To estimate the distribution of thermal neutron flux and gamma-ray dose, neutron irradiation experiments with a water phantom were performed at the iBNCT facility. Gold wires or TLDs were set in the phantom and the phantom was set to irradiation position with beam aperture. Neutron beam of iBNCT facility was irradiated to the phantom. On the other hand, for estimation with Tsukuba-Plan, CT images of the water phantom used in the experiment were loaded to Tsukuba-Plan and the irradiation conditions were represented. The experiment was simulated properly by Tsukuba-Plan, finally two-dimensional distributions for both of thermal neutron flux and gamma-ray dose in the phantom were

determined. The calculation results from Tsukuba-Plan were compared with the experimental values. And dose estimation using CT data for a realistic head phantom were performed with the Tsukuba-Plan in order to confirm applicability of the system to estimation for an actual human body.

[Results and discussions] In the comparison, all calculation values of thermal neutron flux were normalized by fitting the calculation value at the peak point on the beam axis (2 cm in depth) to experimental value of the same point. For the verification with the iBNCT facility, the calculations of the distributions for both of thermal neutron flux and gamma-ray dose were in good agreement with the experimental values, respectively. However, for the gamma-ray dose, absolute values for the calculations normalized by thermal neutron flux value were approximately 20% lower than experimental values. As one of the reasons for this discrepancy, inappropriate primary gamma-ray (photon flux) definition included in the beam source definition of iBNCT installed in the Tsukuba-Plan is considered. And the non-negligible error of the measurement with the TLDs may be attributed because TLDs are affected by neutrons and feeding effect. The primary photon ratio in the source is compensated properly to estimate gamma-ray dose properly. The verification results demonstrated that Tsukuba-Plan enables to perform dose estimation for BNCT performed in the iBNCT facility. Regarding dosimetry with a realistic head phantom, the results demonstrate the system can determine several doses and dose volume histogram (DVH) for each Region of Interest (ROI) for actual dose estimation with a human body.

[Conclusions] To perform BNCT clinical trials using iBNCT device, the University of Tsukuba is developing the Tsukuba-Plan. Based on the verification results, we confirmed that the Tsukuba-Plan can perform to estimate doses properly for BNCT treatment at iBNCT. We carry out further verification in order to use actual treatment and to apply pharmaceutical approval of the system. And in order to confirm the applicability of the Tsukuba-Plan to other BNCT facilities, we are performing same verifications using Kyoto University Reactor (KUR) for the future.

[1] H. Kumada, et al. Project for the development of the linac-based NCT facility in University of Tsukuba. Appli.Radiat.Isot. 2014; 88:211-215.

Keyword: boron neutron capture therapy, dosimetry, treatment planning, Monte Carlo

Pa P2 08

Development of a novel patient setting & real-time monitoring system using motion capture technology for boron neutron capture therapy

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[Introduction] A project team (iBNCT) with University of Tsukuba is developing not only the neutron source device but also several peripheral devices needed in BNCT treatment are being developed. As a part of the development, we are developing a novel patient setting system by utilizing a motion capture technology. In the BNCT, patient's positioning is very important, a patient has to be fixed to irradiation position determined by treatment planning. And the position and posture of the patient must be kept during irradiation. However, it is not easy to keep the position without moving an inch during irradiation because irradiation time of BNCT is a long compared with conventional external radiation therapies. In particular, in accelerator-based BNCT, it may take a long time to irradiation against the reactor-based BNCT due to lower neutron intensity. Thus we thought that a method and device which can monitor the movement and position of a patient during irradiation should be developed, in addition to the method which can guide the patient to the irradiation position before the irradiation. Therefore we have devised to combine a motion capture technology to the system for the setting (guiding) to the irradiation position and monitoring of the position of the patient in BNCT.

[Materials and methods] The new patient's setting & monitoring system is composed of many cameras and software. The prototype of the system has been installed in irradiation room of the iBNCT facility. Here our patient's setting procedure is introduced. First, a patient is set up to a temporary irradiation position with dummy beam port. The dummy beam port is set in the room from approximately 2 m away from actual beam port. Next, the patient fixed to the temporary irradiation position is transferred to the actual irradiation position while keeping its posture. In the setting work, some markers are put on the patient. In the first positioning to the temporary position, the patient is guided by using nine cameras and laser lines. The system with the cameras estimates respective coordinates for the markers and patient's regions such as eyes, hears, nasion and apex of the nose. And the system has recognized ideal (planned) position for each region on irradiation position with the dummy beam port and can calculate the difference of each coordinate between the ideal position and actual position detected by the system. And the

Parallel Session

system indicates the ideal irradiation position where the patient should be there. In the irradiation position after the move to actual beam port, the patient is monitored by using six cameras. The cameras detect in real-time each coordinate of the regions of the patient during irradiation and the system also able to record the coordinates during irradiation.

[Results and discussions] We have carried out a preliminary verification for the prototype system. The system detected each coordinate for some markers. For the measurement accuracy of the coordinates for each marker, the difference between measured coordinates and actual position are less than a few millimeters, respectively. Thus we thought the measurement accuracy of the system for each marker is sufficient, due to our target of the accuracy with each marker is less than 10 mm.

[Conclusion] The iBNCT Project team is developing a novel patient setting & monitoring system. In order to put the system into practical use, further development and verification are still necessary. We expect that practical application of this system will contribute to the improvement of the treatment system of BNCT.

Keyword: boron neutron capture therapy, patient setting, motion capture, treatment planning

Pa P2 09

Effect of fast neutron and gamma-ray ratios on a dose distribution in a water phantom

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Introduction

Accelerator based BNCT facilities have been constructed, and are under construction and planning in the world. In Japan, there are several BNCT facilities based on the accelerators, and some of them are already in a clinical trial stage. To evaluate such neutron sources, it is necessary to re-examine the recommended values in the IAEA TECDOC-1223 published in 2001 since the TECDOC was based on reactor neutron sources. Therefore, we studied the effect of fast neutron ratio and gamma ratio on a dose distribution in a water phantom.

Method

We used calculation code PHITS[1] and JENDL-4.0 kernel[2] for radiation transportation. We selected three representative neutron sources with different fast neutron ratio. As the smallest ratio we chose Nagoya BNCT at Nagoya University, as a medium iBNCT at Ibaraki prefecture[3], and as the largest C-BENS at Kyoto University[4]. We assumed a boron concentration of 25 ppm in a normal tissue and the T/N ration is 3.5. The neutron beam from a BSA of each facility was injected into a water phantom and a dose distribution was calculated. Furthermore, we tried to investigate the effect in more detailed by applying artificially produced fast neutron ratio. Gamma-ray effect was also studied by changing the ratio artificially.

Results

We obtained AD30 (advanced depth at 30 Gy-eq), and AD30 is a little bit large in C-BENS compared with other facilities. However, the maximum dose obtained was smallest at C-BENS. The difference is not so large. Therefore, we investigated the effect in more detail by changing the ratio artificially. It was found that fast neutron up to around several tens keV was useful to enlarge the AD30 value. The recommended value of boundary of the fast neutron may be severe. The effect of gamma-ray ratio reduced the AD30 almost linearly with increasing the ratio.

Conclusion

The results suggest that the dose ratio distribution should be studied to evaluate the BNCT facility performance since it is difficult to know overall performance of the irradiation beam simply by the recommended values of TECDOC-1223.

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Keyword: Irradiation field, fast neutron ratio, gamma ratio, dose distribution, water phantom

Pa P2 10

Radiation quality dependence of polymer gel dosimeters in therapeutic neutron irradiation field

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Introduction

Epithermal neutron irradiation in BNCT utilizes moderation interaction to treat deep-seated tumors. While the thermal neutron flux distribution peaks in deeper region, dose distribution depends on the geometry of the target. To improve the quality of the treatment, it is necessary to verify and validate calculated dose distribution especially in non-referential condition. Polymer gel dosimeters can record three-dimensional (3-D) dose information. The dosimeters are composed of water for the most part and can be formed in anatomically equivalent shape. While these dosimeters have attractive dosimetric features, their response depends on the radiation quality, such as LET. To apply polymer gel dosimeters to neutron irradiation field, the radiation quality dependence of the dosimeters was evaluated in therapeutic neutron irradiation field.

Materials and Methods

Responses of the polymer gel dosimeters to neutron and Co-60 gamma-ray irradiation were compared. Three types of dosimeter were evaluated in this work: (1) standard MAGAT-type polymer gel dosimeter composed of water (87wt.%), methacrylic acid (5wt.%), gelatin (8wt.%) and 2 mM Tetrakis(hydroxymethyl)phosphonium chloride, (2) MAGAT added with 5 mM Li-6 enriched (96at.% Li-6) lithium sulfate and (3) 25 mM boric acid of natural isotopic composition. The dosimeters were prepared in quartz test tubes and placed at 2.5, 5.0 and 7.5 cm depths in 10 cm × 10 cm × 10 cm cubic water phantom in order for the dosimeters to be irradiated with different neutron energy spectra. The neutron irradiations were carried out using the epithermal neutron irradiation mode of Heavy Water Neutron Irradiation Facility at Kyoto University Reactor. The dosimeters were irradiated for 1 and 2 hours during 1 MW reactor operation at room temperature. Monte Carlo simulations were performed using PHITS code. Absorbed dose for the dosimeters was calculated by energy deposition of each secondary charged particle. LET distributions of the absorbed dose were also calculated using T-LET tally of PHITS code. The measured values using gold activation foils and BeO TLDs were utilized to normalize the calculated neutron fluence and gamma-ray dose respectively. The dose-response curves were obtained and the relationship between dose-response characteristics and LET distributions was analyzed.

Results

The response of the three types of dosimeter to Co-60 gamma-ray was almost identical. For neutron irradiations, the dose-response characteristics varied for different types of the dosimeter and neutron energy spectra. The relative efficiency of converting absorbed energy into the dosimeter response decreased monotonically up to one-fifth with increasing dose-mean LET.

Conclusion

The radiation quality dependence of the dosimeter sensitivity was evaluated quantitatively for soft tissue equivalent, Li-6 containing or B-10 containing MAGAT polymer gel dosimeter. With the quantitative evaluation of the radiation quality dependence, the polymer gel dosimeter is applicable to radiation quality evaluation in neutron irradiation fields and to 3-D dose distribution measurement with the correction function.

Keyword: Gel dosimeter, LET depemdence, PHITS

Pa M1 01

A practical handling of the limitation of absorbed dose in BNCT

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Background and Purpose
The opportunity of Boron Neutron Capture Therapy (BNCT) is extended more likely by the realization of the accelerator BNCT irradiation system. The approval examination of the Pharmaceutical Affairs Law and Pharmaceutical & Medical Device Act has been carried out based on regulatory science. When this standard is indicated precisely, BNCT has little way to be approved because of the feature of dose evaluation. Based on these situations, a practical handling of the absorbed dose in BNCT should be managed for the continuous development of it.

Features of absorbed dose evaluation
The characteristic of the absorbed dose in BNCT is raised from evaluating procedure which is divided into (i) cell level and (ii) organ level. (i) Cell level: This is related to both merit and weak point of BNCT. The characteristics are (a) α particle and 7Li nucleus generated by the reaction of 10B(n, a) 7Li release energy intensively in a same range as a cell, (b) The average number of α particles and 7Li nuclei in BNCT is less than ten which follows the Poisson statistics in a cell, and (c) The absorbed dose of a cell nucleus related to the life and death of the cell is depended on intracellular boron density and its distribution and also its time change greatly. The strict absorbed dose evaluation is impossible for cell level. (ii) Organ level: The distribution of the neutron flux in a living body decrease towards a deep part from the peak. Therefore, it is necessary to decide a neutron exposure dose while keeping lower than the tolerable dose of the normal organ around the tumor. This is the reason where the tumor of the deep part cannot be treated. In addition, it is related to the second carcinogenesis of a normal cell surviving in a tumor part.
Summary
(A) The limit of the absorbed dose evaluation for the cell level in BNCT should be informed honestly with the minds of “open, fair, honest” for patient first. BNCT has been established by a boron compound and the dosage method in the protocol using average data provided through much fundamental experiments and clinical studies for curative effect and the side effect using the calculated neutron exposure dose. The CBE factor which considered the uptake mechanism to the tumor part of the boron compound has been used for the dose evaluation. However, there is vague condition in the absorbed dose evaluation at cell level in the BNCT.
(B) The measurement system of absorbed dose distribution during BNCT. At present, boron distribution data measured by the PET image analysis using 18F-BPA can be evaluated beforehand. And the absorbed dose distribution of the organ level is estimated with the calculated neutron flux distribution. But measurement data during BNCT has been short. The relationship between the measured absorbed dose data of a organ level and the curative effect can be explained more clearly. It will particularly help for getting the understanding of the person concerned.

Keyword: BNCT, limitation of absorbed dose, practical handling, philosophy

Pa M1 02

Development of Proton Linear Accelerator based Boron Neutron Capture Therapy System in Republic of Korea

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Introduction:
In 2016 Korea BNCT national project began. For the new technology development of Proton Linear Accelerator-based Boron Neutron Capture Therapy (A-BNCT) facilities and a treatment plan system, well qualified and experienced laboratories, companies and hospitals need to be collaborated. Thanks to the great cooperation and collaboration with Dawonmedax, Dawonsys, POSTECH, Korea Basic Science Institute, Seoul National University, Gachon University, Gil hospital, and Korea Atomic Energy Research Institute, the A-BNCT facility made by our country was constructed.

Material and methods:
A-BNCT facility has been being installed at Songdo BNCT center since Dec. 2017. And now we are preparing preclinical study of BNCT in 2018. A-BNCT facility by Dawonmedax consists of a high power proton linear accelerator (10MeV), a high current proton injector, a radio frequency quadrupole (RFQ), a drift tube linac (DTL), beryllium target systems and moderator assemblies with three beam lines and tree treatment rooms. It has a capability of production of higher epithermal neutron flux and lower residual radiation doses than the IAEA BNCT recommendation. And we are developing treatment planning system (TPS) based on industry-academic cooperation. Previous multiple BNCT clinical trials I/II in Japan, Sweden, Finland, Czech Republic, US, Taiwan, Germany, Italy, Netherlands and Argentina represented the favorable survival and improved quality of life in patients with glioblastoma, melanoma and head and neck cancers compared with conventional therapies. And the treatment response of variable refractory diseases such as ma-

lignant mesothelioma, extra-mammary Paget's disease, hepatoma and osteosarcoma were good. However, the neutron source of those clinical trials were from nuclear reactors. The utilization of nuclear reactor for BNCT has been difficult in Korea. Therefore, the development of A-BNCT in Korea will open new era with a typical specification therefore we can develop variable clinical applications conveniently in hospitals.

Results:
The therapeutic effect of BNCT is depend on the delivery of boron compounds and neutron flux to tumors. Therefore, multiple studies have been performed and will be done including phantom study for radiation dose, in vitro cell study of boronophenylalanine (BPA), in vivo pharmacokinetics and pharmacodynamics of BPA, effectiveness trial of BNCT using animal tumor model and clinical trials to obtain the approval of Korea Food & Drug Administration.

Conclusions:
Our collaboration teams of A-BNCT in Korea will perform preclinical study and clinical trials sequentially.

Keyword: Korea, BNCT system, proton, linear accelerator

Pa M1 03

Cherenkov radiation and its application in Boron Neutron Capture Therapy

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Introduction: Cherenkov radiation has been explored as a tool of quality assurance in conventional photon radiotherapy. It can also be generated in boron neutron capture therapy (BNCT). The goal of this work was to investigate the emission of Cherenkov photons and its potential applications in BNCT.

Materials and Methods: Monte Carlo toolkit Geant4 was used to simulate the process of neutron transportation and the generation of Cherenkov radiation. A tumor-contained phantom was constructed for simulation the process of BNCT treatment with an epithermal neutron beam. The neutron spectrum obtained from an accelerator-based BNCT facility, which is currently under construction by Neuboron Medtech Ltd in China, was used in the study. The number of Cherenkov photon in the scoring region with various boron concentration distribution and neutron beam characteristic were obtained.

Results: The total number of Cherenkov photon and the number of Cherenkov photon generated by secondary charged particles of gamma rays are equal, which indicates that the Cherenkov photon is generated through secondary charged particles of gamma rays. The contribution of Cherenkov photons generated by secondary charged particles of 2.223 MeV gamma rays is about 74.6% in soft tissue. The contribution of 0.478 MeV gamma rays is less than 0.2%, whereas the contribution of other gamma rays is about 25.3%. The number of generated Cherenkov photon in the phantom slightly decreases with the increase of boron concentration. There are significant changes of Cherenkov photons distribution in the phantom under different neutron beam characteristics.

Conclusion: Cherenkov photons can only be generated from secondary charged particles of gamma rays in BNCT, in which the 2.223 MeV prompt gamma rays are the main contributor. The distribution of Cherenkov photons only can be observably changed by neutron beam characteristics. Thus, Cherenkov photons may have potential for monitoring the stability of neutron beam in BNCT.

Keyword: Cherenkov photons, boron neutron capture therapy, neutron beam, boron concentration

Pa M1 04

Strategies for consistently assessing the response of radiochromic film using flatbed scanners

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Introduction
Radiochromic film has been widely used in conventional radiation therapy, and was proposed as a potential tool for the quality assurance of neutron beam in BNCT. When assessing the radiation response of the radiochromic film, significant uncertainties can be introduced due to many factors. This study was aimed to study influences of scanning settings and inter-scan variability on film response, and then proposed an optimal strategy for consistently assessing the response of radiochromic film.

Materials and Methods
HDV2 films from a single production lot (11171601) scanned by the Epson 12000XL scanner was studied. The scanning setting (i.e. parameters that will be fixed conditions for scanning) was investigated, including usage of a masking sheet, selected scanning resolution and selected focus setting. The studied inter-scan variability includes four influencing factors, i.e. outside illumination intensity, film homogeneity, scanning position, and operating temperature.

Results
In the study of influences of scanner settings, the usage of a masking sheet with a square hole can shield the scattered light, fix the film position, and prevent the film from curling. We found that multipeak distributions of pixel values of films existed at some high dpi settings (above 600 dpi), and selected 2000 dpi as the optimal dpi setting with nearly Gauss distribution and multipeak problem free. By adapting the focus position of the scanner, the relative standard deviation of pixel values reduced by 36%–50% in three color channels while the mean value kept constant. In the influence study of inter-scan variability, outside illumination was found to be unrelated to the film response. According to the investigation of scanning position and film homogeneity, scanning the same film before and after irradiation was recommended. The suitable operating temperature range for the scanner was found to be 15–24°C, which provides stable film response assessment. Finally, a standard operating procedure for response assessment that can help other researchers study more scanners, films, and particle types was introduced, will be presented in the conference.

Conclusion
The influence of scanning setting and inter-scan variability on the response uncertainty was determined, and strategies for consistently assessing the response of radiochromic film was proposed. The proposed standard operating procedure of the study offers the possibility to accurately assessing the film response by other researchers for more scanners, films and particle types.

Keyword: Radiochromic film response, Scanning setting, Inter-scan variability, Standard operating procedure

Pa M1 05

Current Status of BNCT Clinical Trials in Japan

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Over the past several years, expectation for feasible commercial accelerator-based BNCT (AB BNCT) systems appears to be growing. Instead of reactors, nuclear reactions of elements with accelerated particles, typically protons, have been regarded as a realistic alternative for neutron source for BNCT. A major advantage of AB BNCT systems is that particle accelerators are much easier and safer to operate and maintain compared with a reactor-based systems, especially in a hospital environment.
Brookhaven National Lab (BNL) and Massachusetts Institute of Technology (MIT) in the United States were pioneers of clinical BNCT since 1951. Clinical trials were conducted under their leadership using reactors, and some of the accelerator facilities explored the use of existing accelerators for BNCT in 1990s and 2000s. Japan has been deeply involved in BNCT development since the late 1960s. This research also originally used research reactors. In the 2000s, Kyoto University Research Reactor Institute (KURRI), Kumatori, Osaka, Japan, Stella Chemifa Corporation (SC), a Japanese high-purity chemicals supplier, and Sumitomo Heavy Industries, Ltd. (SHI) agreed to develop an AB BNCT system. SHI installed a 30MeV cyclotron at KURRI in 2009. Meanwhile, SC set up Stella Pharma Corporation (SP), a pharmaceutical subsidiary of SC and a boron compound (boronophenylalanine or BPA) provider. Thus SHI and SP started a Phase I clinical trial in cooperation with KURRI and Osaka Medical Collage (OMC), Takatsuki, Osaka, Japan, for Brain tumor in 2012, and another Phase I clinical trial in cooperation with KURRI and Kawasaki Medical School (KMS) for Head & Neck (H&N) cancer in 2014.
After successful evaluation of safety at Phase I for the above-mentioned clinical trials, SHI and SP initiated Phase II in 2016. At that time Southern Tohoku General Hospital (STGH) in Koriyama, Fukushima, Japan, and National Cancer Center Japan (NCCJ) joined the Phase II. The set numbers of patients in Phase II are 21 for H&N cancer and 24 for Brain tumor, respectively. Primary endpoint for H&N cancer is the response rate after

3 months of irradiation in reference to RECIST (Response Evaluation Criteria in Solid Tumors). For Brain tumors, it is the survival rate after 12 months of irradiation. As of this abstract submission, patient irradiation has nearly completed.
Secondary endpoint is two-year follow-up observation after treatment prior to the government review. Therefore, the current perspective on the submission of medical device and drug application will be in 2020. In 2014, the Ministry of Health, Labor and Welfare (MHLW) announced the "Strategy of SAKIGAKE" to lead the world in the practical application of innovative medical products and expedites Pharmaceutical and Medical Device Agency's (PMDA) review process for designated items. SHI's AB BNCT system and SP's boron compound will be reviewed according to this SAKIGAKE designation system. The challenging part of the regulatory process will be that the BNCT system is a combination product, which means both the device and the drug need to be approved at the same time.
In this presentation, we will show our on-going developmental efforts for a realistic treatment system to bring BNCT to a clinical forefront in the not-too-distant future.

Keyword: accelerator-based BNCT, clinical trials

Pa M1 06

Preparation of Water-in-Oil-in-Water Emulsion as Drug Delivery System Using Mixing Medical Device for Neutron Capture Therapy

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[Introduction] Most hepatocellular carcinoma (HCC) cases are considered to be incurable, and there are only few treatment options for prolonging survival. We consider boron neutron capture therapy (BNCT) as one of the multidisciplinary treatments for HCC. For effective BNCT, it is necessary to deliver boron compound to HCC tumour tissues full of blood vessels, and to maintain constant concentrations of 10B atoms in the cancer cells. We had developed a 10B sodium mercaptododecaborate(10BSH)-entrapped water-in-oil-in-water(WOW) emulsion (10BSH-WOW), and evaluated it as a selective boron carrier for the possible application of BNCT for HCC, which could be an option for patients who cannot be treated with conventional therapies. The WOW was prepared using a double membrane emulsification technique involving a controlled pore glass membrane. The technique needs approximately six hours or more; so we aimed to develop the medical device, which makes it simpler and easier to produce equivalent WOW emulsion compared to conventional making instrument.

[Materials and Methods] In this study, we developed the syringe-shaped medical device which we attached SPG Millipore Filter. 10BSH (262.5 mg) was dissolved in 1.5ml of a 5% glucose solution, which was filtered through a first SPG controlled pore glass membrane and then emulsified in 1.5 ml IPSO containing surfactant to form the water-in-oil emulsion (WO). The WO emulsion was then emulsified again with an aqueous phase containing 3 ml saline solution and surfactant through a second SPG controlled pore glass membrane using this medical device. The shape of the WOW emulsion was observed using an optical microscope, and the particle size distribution of the WOW vesicles was determined using a SALD-2000 laser diffraction particle-size analyzer. As a part of the safety evaluation of 10BSH-WOW, a single dose toxicity study was conducted by hepatic arterial administration to 3 male rabbits at 0.075 and 0.15 mL/kg as 10BSH-WOW in rabbits to investigate toxicity profiles.

[Results] By using this device, we were able to make the WOW emulsion of the single peak of 70 μm similar to the past. We were able to produce the WOW emulsion of the

Parallel Session

same size even after changing the persons who perform the experiment more than approximately ten times. Single-dose toxicity study by intra-arterial injection of 10BSH-WOW in rabbits was performed. As a result, there were no test article-related changes in any of the BSH administration groups in surviving animals. It is thought that the side effects were absent by human conversion if it was administration 7.5 ml or less. We were apparently able to relieve side effects like the administration to whole liver in rabbits more than the perform hepatic arterial infusion of 10BSH-WOW in human cases, because we perform the administration super-selectively by catheters.

[Conclusion] We developed the syringe-shaped medical device which we attached SPG Millipore Filter. By using this device, we were able to make the WOW emulsion of the single peak of 70 μm similar to the past. Single-dose toxicity study by intra-arterial injection of 10BSH-WOW in rabbits was performed, and the side effects were not seen. We will take the approval as the medical equipment in Japan and foreign countries and hope to advance to the preclinical & clinical studies of BNCT by intra-arterial infusion of cancer selective 10B compound as multidisciplinary treatments for HCC in near future.

Keyword: Hepatocellular carcinoma, WOW emulsion, Intra-arterial injection, BNCT

Pa M1 07

Development of remote-changeable Bonner sphere spectrometer

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[Introduction] In general neutron energy spectrometer using Bonner sphere, the moderator covering a neutron detector is made of solid material such as polyethylene, and several moderators with several diameters should be prepared. It is necessary to enter the irradiation room for changing the moderators several times. Also, the normal Bonner sphere has the flat and wide peak of the response function in the epithermal neutron region. We are developing remote and online evaluation-method of neutron energy spectrum by Bonner sphere. The spectrometer using Bonner sphere use liquids such as pure water or boron acid water as moderator. Multilayered concentric spheres having multiple spherical shells are prepared. The moderator can be changed without entering irradiation room by remote control supplying and draining moderator liquid for each shell. LiCAF detector is used as an online neutron-detector. The development of this remote-changeable Bonner sphere spectrometer is reported.

[Materials and Methods] Simulation calculation is performed for the development of the spectrometer. Ten types of acrylic container for Bonner sphere is assumed. These container have five hollow shells for supplying moderators and acrylic walls. The thicknesses for the shells and walls in each container are 1cm&1mm, 1cm&2mm, 1cm&3mm, 1cm&4mm, 1cm&5mm, 2cm&1mm, 2cm&2mm, 2cm&3mm, 2cm&4mm and 2cm&5mm. Moderators are pure water and boron acid water (0.14wt%, B-10 solubility at 20 degree centigrade). Thirty-three combinations for the shells and moderators are simulated. For the ten combinations, only one shell is filled with pure water or boron acid water, and the remaining four shells are empty. For the twenty three combinations, the shells are filled with the moderators in turn from the central shell. Totally, 330 patterns for the spectrometer are simulated. In the first step, the response functions for 330 patterns are calculated using a Monte Carlo simulation code, Phits. The energy range for the incident neutrons is assumed to 1 x 10-10 to 1 x 102 MeV. 120 energy bins are set dividing the energy range at equal intervals in logarithmic scale. In the second step, the neutron energy spectra for the respective response functions are estimated. In the third step, the minimum and optimum combination for the shells and moderators with high-independency for the estimated spectra is selected by a maximum likelihood method with truncated singular value decomposition, named “High Independence Selection (HIS)”. In the final step, the selected combination is verified by simulation.

[Results] As of April 2018, the calculation for the response functions is an ongoing process.

[Conclusion] 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.

Keyword: Boron neutron capture therapy, Bonner sphere spectrometer, Neutron spectra, LiCAF detector,

Pa M1 08

REACTOR LABORATORY FOR BIOMEDICAL RESEARCH IN THE NATIONAL CENTRE FOR NUCLEAR RESEARCH, POLAND

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Introduction
The National Centre for Nuclear Research (NCBJ) is working on the adaptation of the H2 channel, one of the MARIA Research Reactor's horizontal channels. The beam derived from it will be a tool for performing preclinical and developmental studies in biomedical aspects (including BNCT therapy).

Methods
While the interest in the therapy increased and the works on construction of the research stand at the Reactor started, the cooperation between people from Polish scientific society is being built. At the moment of writing this abstract, 16 institutions such as research centres or oncology centres declared their intent of membership. Through the group meetings organized on the basis of scientific workshops and their involvement in biological, chemical, medical and material research the idea of creating an interdisciplinary laboratory has appeared.

Results
We have a thriving multidisciplinary team operating on behalf of the institute working on emerging the station. The construction and computing research groups are working on the interior of the channel, i.e. a converter, an intermediate channel and a Beam Shaping Assembly, BSA. The dosimetry group works on the beam characteristics at each stage of the project and protects the radiological situation in the room. Another section is the biomedical research group providing infrastructure for conducting scientific and preclinical studies. In January 2018 the "Reactor laboratory for biomedical research" was launched at NCBJ. It is a place where such a multidisciplinary team will fulfil their research projects. In April 2018, we are at the stage of creating a functional plan of the building, which covers five main areas of research, i.e. biology-radiobiology (1), dosimetry-radiation protection (2), chemistry-radiochemistry (3), physics (4) and medicine (5).

Conclusion
In the first step, the laboratory will support our institutional team of specialists and scientists from the above-mentioned fields of science. Thanks to our experience in physics and dosimetry, knowledge and experience of our partners in the field of biology and

chemistry, we create our competences in the field of radiobiology. The second step and task in the emerging laboratory will be to create a team that is fully substantive and able to conduct extensive pre-clinical research in the field of therapy, still cooperating with our inter-university team. The last aim will be implemented in cooperation with oncologists from several medical centres in Poland (by now Lukaszczyk Oncology Centre and a few Military and University Medical Institutes).

Keyword: radiobiology, dosimetry, BNCT

Pa M1 09

The overview and prospects of BNCT facility at Tsing Hua Open-pool Reactor

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The BNCT facility at Tsing Hua Open-pool Reactor (THOR) started construction in 2000 and was completed in 2004. After commissioning test and pre-clinical study it went to clinical trials since August 11, 2010. Up to now it has carried out two clinical trials of recurrent head and neck cancer patients. For the first protocol of the clinical trial there were 17 patients, each patient underwent two fractions of treatment with an interval of one month. There were 9 patients in the second protocol, each patient underwent one fraction of treatment and one month later received a 50-Gy make-up dose by IMRT. Since last year it launched into emergent (compassionate) treatment of patients with a variety of cancers. In this paper an overview of the BNCT facility at THOR will be elaborated at first. The whole picture will be presented which consists of the following aspects: the construction project, the beam quality, routine operations including the QA program for the beam delivery, determination of B-10 concentration in blood and T/N ratio, the clinical affairs including the patient recruit procedure and the patient irradiation procedure.

The prospects of the BNCT facility at THOR are that it is a facility for conducting clinical trials, emergent (compassionate) treatments, radiobiological studies, beam dosimetry research and development, new drug development and animal tests. The facility is open to the community all around the world.

Keyword: BNCT facility, THOR, overview, prospects

Tuesday, October 30, 2018

Pa Ch2 01

New self-assembling peptide Drug Delivery System with BSH toward clinical application

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[Introduction] Glioblastoma multiforme (GBM) is the most common malignant central nervous system primary tumor, and not curable. BNCT (boron neutron capture therapy) is the effective treatment against GBM in present multimodal therapy. In BNCT in GBM, one of the keys to success can depend on the boron compounds. The adequate boron delivery into all of every tumor cells is essential for BNCT to GBM. The combination of BSH and BPA in clinical GBM BNCT showed very good results and that meant the multi boron use in BNCT was one answer to next step of BNCT. In this time, we showed results of the new self-assembling peptide DDS with BSH toward clinical application.

[Materials and Methods] The self-assembling A6K peptide (chemical formula: AcAAAAAAK-CONH2 (+1)) was found and reported by Dr. Shuguang Zhang, MIT in 1982. The A6K peptide showed self-assembling feature in water, and worked as drug delivery system of siRNA with only mixture. The A6K drug delivery system was approved as clinical use in Japan, and recently the A6K/RPN2 siRNA complex was used for breast cancer clinical trial since 2015. We selected A6K peptide as new boron delivery tools and made the combination of A6K and BSH. We observed the complex of A6K and BSH with scanning electron microscope in different mixture ratio. Next, we checked the cell toxicity with WST-1 assay and measured intracellular boron concentration in each different drug concentration and time course. Finally, we administrated BSH or A6K/BSH complex against mouse brain tumor model through tail vein injection and observed BSH localization in immunohistochemistry with anti-BSH antibody.

[Results] At first, we established the simple A6K/BSH complex making method, as just mixture the BSH and A6K water solution by itself. The BSH/A6K complex with different mixture ratio showed different shape and different diameter of complex in SEM image. We decided the particular mixture ratio of A6K/BSH, 1:10 mol ratio, complex as the most fitted for drug delivery system to brain tumor. The ideal range of particle size of DDS is 20nm to 200 nm, and ours' complex diameter was about 40nm. Next, we administrated BSH/A6K complex to human glioma cell lines and measured intracellular boron uptake. The intracellular boron concentration with BSH/A6K complex in U87 delta EGFR was 10 times or more higher than that with BSH. We reconfirmed the particular mixture ratio of BSH/A6K, 1:10 complex as the most fitted for drug delivery system to brain tumor. Finally, we administrated BSH or A6K/BSH complex through mouse tail vein and got brain tumor sample after 12hr. The A6K/BSH mouse brain sample showed specifically accumulated BSH in tumor area, but BSH brain sample did not show BSH accumulation.

[Conclusion] A6K peptide is clinical use in DDS and will spread various drug delivery tool for various clinical fields in future. Our A6K/BSH complex is very promising boron drug for next generation BNCT and the combination of A6K/BSH and BPA will bring new effect to GBM BNCT.

Keyword: peptide, DDS, BSH, brain tumor, nano particle

Pa Ch2 02

Development of closo-dodecaborate-containing water-soluble folate derivatives targeting to folate receptor α for boron neutron capture therapy

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<Introduction>
Boron neutron capture therapy (BNCT) is based on the nuclear reaction of 10B with ther-

mal neutrons yielding α particles in tumor cells. L-BPA is now used in Phase II clinical trials of accelerator-based BNCT for glioblastoma and head and neck cancer. It has been observed that L-BPA is taken up by cancer cells via L-amino acid transporter (LAT1) that is overexpressed on the surface of many cancer cells. However, there are still many patients who are not able to receive it due to their L-BPA negativity. We focused on folate receptor α (FRα) that is often highly expressed on many cancer cells. We considered that the boron cluster-conjugated folate derivatives would be efficiently taken up even by cancer cells not overexpressing LAT1.

<Materials and Methods>
We designed and synthesized novel closo-dodecaborate-containing water-soluble folate derivatives, PBC1-4 based on the coupling reaction between pteroyl azide and closo-dodecaborate-conjugated amine or amino acid derivatives. The synthesized compounds were subjected to boron uptake experiments using HeLa, MCF-7, and U-87 MG cells as FRα positive cancer cell lines, and A549 cell as a FRα positive cancer cell line. Boron concentration in cells were determined by ICP-OES.

<Results>
PBC1-3 were found to accumulated efficiently in FRα positive cancer cells than in FRα negative cancer cells. Furthermore, they accumulated more efficiently in U-87 MG cells that are FRα positive and LAT1 negative, than BPA.

<Conclusion>
These results suggests that PBC1-3 are potential candidates for treatment of patients with FRα positive and LAT1 negative cancers in BNCT.

Keyword: LAT1; FRα; folate derivatives; closo-dodecaborate

Pa Ch2 03

Development of Boron-Containing Monosaccharide Derivatives for Boron Neutron Capture Therapy

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Boron neutron capture therapy (BNCT) is one of the cancer radiotherapeutic methods that is considered to induce smaller damage to normal tissues than tumor tissues [1]. Boron-10 (10B) containing compounds that can be accumulated in tumor tissues are expected as suitable agents for BNCT. For the design of successful BNCT agents, the following criteria must be satisfied: (i) low toxic and higher uptake in tumor tissue than healthy normal tissue; (ii) 10B must be accumulated in tumor tissues, but rapidly cleared from blood and normal tissues; and (iii) the concentration of boron inside or near tumor cells must be > 109 10B atoms/cell (20-35 mg 10B/gram of tumor tissue). The major requirement in the development of boron delivery agents is the selective and sufficient delivery of boron compounds at the tumor sites with minimal toxicity to normal tissues. Although the various boron containing compounds such as amino acids, nucleosides, and polyamines derivatives have been reported, only two boron drugs, BSH (sodium mercaptoundecahydrododecaborate, Na2B12H11SH) and BPA (L-4-boronphenylalanine), have been recognized as clinically test agents [2]. Therefore, discovery of new BNCT agents is highly required for the acceleration of cancer treatment.
In this work, we have focused on the glucose metabolism in tumor cells to design the new BNCT agents. It is generally accepted that glucose transporter (GLUT) is highly expressed on the cancer cells to uptake D-glucose more than normal cells, which is known as the Warburg effect [3]. Besides, it has been reported that the hydroxyl groups of D-glucose play role in hydrogen bonding interactions with various amino acid residues of glucose transporter type-1 (GLUT-1) [4]. These findings prompted us to develop the new boron-containing compounds based on D-glucose scaffold for BNCT.
In this context, we will report on the design, synthesis and biological activities of boron-containing monosaccharides. It has been found that boron containing sugars are internalized into HeLa S3 and A549 cells, as determined by the inductively coupled plasma-mass spectrometer (ICP-MS). In this presentation, these results will be reported.

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Keyword: glucose, GLUT

Pa Ch2 04

Dodecaborate-sugar conjugates as delivery system for BNCT

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Introduction: 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.
As new neutron sources, cheaper and more acceptable by the public than nuclear reactors such as accelerators, are becoming available, the interest towards new and more selective agents, specific and effective against tumor cells is currently raising.
Our group is working for a long time on the development of sugar conjugated to boron containing moieties, e.g carboranes, and their use as components of nanovehicles.
We decided to focus our recent research on the synthesis of new sugar-derived structures, containing 10-B atoms in a different form for selective tumor targeting exploiting active transport.
In fact, carborane-sugar conjugates have amphiphilic properties, which can be exploited for their formulation in delivery systems such as liposomes but limits a more general use.

Materials and methods: the synthesis of the sugar derivatives presented here exploits the reactivity of the oxonium-dodecahydro-closo-dodecaborate derived from dioxane, easily obtained by reaction of sodium dodecahydro-closo-dodecaborate with dioxane in the presence of hydrogen chloride. Nucleophilic ring opening with isopropylidene-protected glucose, galactose and fructose gave the corresponding protected conjugates. Last deprotection step with trifluoroacetic acid afforded the free, water soluble final compounds.

Results: the nucleophilic ring opening of oxonium-dodecahydro-closo-dodecaborate has been previously described with a variety of nucleophiles, including alkoxides. However, the reaction is usually performed using a large excess (ten fold) of nucleophile, which can be acceptable for simple and cheap alcohols but is not practical even for slightly complex and more expensive hydroxy compound. In addition, non-volatile compounds introduce purification problems to products already not easy to handle.
We changed the reaction stoichiometry and demonstrate that such a large excess is not necessary as the reaction occurs smoothly with 2 equivalents of the sugar alcohol.
The opening product is easily isolated as cesium salt and is ready to be deprotected at the sugar moiety. We encountered some difficulties in the deprotection step. In fact, benzyl groups demonstrated to be very reluctant to react under standard hydrogenolysis conditions, we opted for isopropylidene-protected sugars and we were able to perform the final deprotection.

Conclusion: we developed a fast, efficient and scalable approach to dodecaborate-sugar conjugates. The compounds will be tested for their toxicity and in preliminary cellular uptake essay.

Keyword: dodecaborate, sugar, synthesis

Pa Ch2 05

Microfluidic technology for the synthesis of liposomes encapsulating boron compounds in Argentina

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Introduction
A recent research line of the Argentinean BNCT Project is related to the design and development of nanovehicles as boron compounds carriers by microfluidic technology. Targeted-nanovehicles allow to take advantage of the distinctive characteristics of tumor microenvironment in order to enhance passive and active drug delivery. From all types of nanovehicles, our research has been specially focused on the development of liposomes, since they have become the most commonly approved carrier for drug delivery in human patients. In particular, our group is currently developing boron compounds-loaded liposomes decorated with Trastuzumab as antibody-targeted nanocarriers for the potential application of BNCT to HER2 breast cancer subtype.

Materials and methods
As part of our previous research, nano-sized liposomes encapsulating boron compounds

were obtained by means of the film lipid hydration method. This conventional method is poorly efficient, and involves considerable processing time since several extrusion steps must be performed to yield appropriated particle size and polydispersity. Microfluidic-assisted synthesis of liposomes has recently emerged as a powerful technique to overcome these shortcomings, featuring exquisite micromixing conditions (due to the laminar regime in which these systems usually operate) and enabling the efficient and reproducible production of monodisperse populations without postprocessing. Another key advantage of the microfluidic technology is that it enables the control of the vesicle size by easily modifying the fluidic parameters.
Recently, we have designed, fabricated, and characterized different poly methylmethacrylate (PMMA) microfluidic chips for the insertion of the amphyphilic boron compound Lactosyl-carborane in liposome bilayers. Different flow rate ratios (FRR) between the organic phase and the aqueous phase were evaluated in order to optimize particle size.

Results
Microfluidic technology allowed to obtain monodisperse liposomes with a mean diameter of 89.58 ± 0.94 nm (PI = 0.176 ± 0.011) together with a boron encapsulation efficiency approximately 50% higher than those obtained with the traditional method. In addition, processing time using the microfluidic method was significantly lower.

Conclusion
The microfluidic technology is a field growing very rapidly, with a wide range of applications in other areas relevant to drug delivery using nanovehicles such as chemotherapy and genetic therapy. Besides BNCT applications, our group is also currently working in the microfluidic-assisted synthesis of oxaliplatin-loaded liposomes and siRNA/PEI nanocomplexes respectively.
In this work, we present the results of both methods for the synthesis of liposomes for BNCT together with the microfluidic system capability of our group for other applications.

Keyword: liposomes, lactosyl-carborane, microfluidics

Pa R1 01

Hybrid gold and boron nanoparticles for treatment and boron dose estimation in boron neutron capture therapy for malignant glioma

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Introduction
Boron neutron capture therapy (BNCT) exploits the release of alpha-particles inside tumor tissues that provide the main effect but direct measurement of this absorbed dose is impossible. For this reason, neutron activation of golden foils placed in proximity to the irradiated samples is typically used as a proxy. With this method, accumulation of radioactive 198Au isotope and measurement of the released 411 keV gamma-rays within the 2.7-day half-life provides neutron capture data. We therefore propose a novel approach of using both boron and gold in the form of composite nanoparticles for direct, in situ absorbed dose evaluation in tumor tissues. Our objective was to develop an in-sample, absorbed dose estimation method using gold and boron compounds accumulated in glioma cells and to design and develop hybrid nanoparticles for direct dose estimation.

Materials and Methods
Human glioma T98G cells were incubated with gold nanoparticles (GNPs, 50 ppm) and boron-phenylalanine (BPA) at boron concentrations of 0, 10, 20, 40 ppm over 24 hours. The control group contained boron without gold. Cells were irradiated in vials with 1 ml of initial boron and/or gold-containing medium in a rotating acryl glass phantom under the neutron producing target of the accelerator-based neutron source at the Budker Institute of Nuclear Physics. Epithermal neutron irradiation lasted 2-3 hours with 2.0 MeV proton energy and 2-3 mA proton current to achieve 6 mAh of overall irradiation. Sam-

ples with GNPs were analyzed by gamma spectrometer. Colony-forming assays (CF-assays) were done two weeks post-irradiation and colonies of ≥50 cells were counted.
A novel method of cascade ultrasonic dispersion / destruction of micron particles was applied to obtain composite boron nanoparticles using water as a dispersion medium. Degradation of large boron crystallites with ultrasound and formation of <100 nm nanoparticles were studied using X-ray crystallography, dynamic light scattering (DLS) and transmission electron microscopy (TEM). Gold and boron concentrations in compounds and cells were measured by inductively-coupled plasma atomic emission spectroscopy (ICP-AES).

Results
At the initial stage of experiments, accelerator-based neutron source efficacy in producing nuclear capture reactions was proven by exponential decrease in colony formation as boron concentrations increased. These results were in line with those previously obtained at the nuclear reactor in Tokai village. Presence of GNPs did not significantly influence the neutron irradiation effect on BPA-enriched cells. Sample activation resulted in radioactive 198Au isotope generation which was utilized for absorbed dose calculations at each boron concentration. We propose the following formula for absorbed dose calculation: D=(k*N*n)/m, where D is the boron dose in GyE, N in the number of activated gold atoms, n is the boron concentration in ppm, m is the mass of gold in grams, and k is the coefficient, calculated depending on the depth (cm) to the sample in the acryl phantom. According to this methodology, cells with 129.8±7.3 μg of gold could obtain 12.98 GyE of radiation. We have also designed and refined composite boron-gold nanoparticles with a novel production method and analyzed their properties in irradiation experiments.

Conclusion
We are the first to develop an in-sample, absorbed dose estimation method using gold and boron compounds accumulated in glioma cells. We also introduced hybrid gold and boron nanoparticles and showed their role in both tumor ablation and direct irradiation dose measurement. We believe such nanoparticles can be further applied to visualize composite boron compound distribution in tumor tissues via isotope scanning or single photon emission spectroscopy (SPECT) to provide data on absorbed neutron dose during BNCT.

Keyword: glioma, nanoparticles, gold activation, absorbed dose calculation, accelerator-based neutron source

Pa R1 02

Electroporation to optimize boron targeting for Boron Neutron Capture Therapy (BNCT): a study of boron biodistribution with Boric Acid in the hamster cheek pouch oral cancer model

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Introduction: The biodistribution of boron carriers in tumor in terms of absolute and relative 10B concentration, retention in tumor, targeting homogeneity and microdistribution conditions the therapeutic efficacy of BNCT. We previously demonstrated the potential of Electroporation (EP) to induce an increase in tumor boron uptake employing sodium decahydrodecaborate (GB-10) -a chemically non-selective boron compound- in the hamster cheek pouch oral cancer model. It is of great relevance to optimize the biodistribution of boron compounds authorized for their use in humans, thus bridging the gap between research and clinical application. Within this context, the aim of this study was to evaluate if EP can be used as a non-specific drug delivery system to optimize the delivery of the boron compound Boric Acid (BA), improving the therapeutic efficacy of BNCT in the hamster cheek pouch oral cancer model.

Materials and methods: Exophytic tumors (Squamous Cell Carcinoma) were induced in the pouch of 10 Syrian hamsters by topical application of the carcinogen dimethyl-benzanthracene (DMBA) twice a week for 3 months. We performed electroporation experiments in tumors (1000 v/cm, 8 pulses of 100μs) as part of 2 protocols employing BA (50 mg 10B/kg iv) varying the time between EP and the administration of the boron compound: (1) BA (t = 0 min) - Early EP (t =10 min) - sacrifice (t =3 hs); (2) BA (t =0 min) – Late EP (t =2.5 hs) – sacrifice (t =3 hs). As a control, the previous biodistribution study with BA (50 mg10B/kg iv, 3-4 hs) without EP performed in the same experimental model was used. Samples of blood, tumor, precancerous tissue and normal pouch tissue, liver, kidney and spleen were processed by sulfuric-nitric acid 1:1 digestion at 100ºC for 1h for ICP-OES boron measurements. In addition, samples were excised and sectioned

using a novel procedure to include the Tumor, the Insertion zone and the surrounding Precancerous tissue in a single section (TIP section), to study boron microdistribution using the neutron autoradiography technique.

Results: We observed a statistically significant increase ($p < 0.0001$) in boron uptake in tumors corresponding to the protocol BA + Early EP (47+/-10 ppm) versus control BA without EP (36+/-7 ppm), whereas for the BA + Late EP protocol boron tumor uptake (35+/-9 ppm) was similar to the control BA without EP (36+/-7 ppm). Both EP protocols, Early and Late, caused a statistically significant increase ($p < 0.0001$) in blood boron concentration compared to the control BA without EP, from 15+/-2 ppm (control) to 52+/-14 ppm (BA + Early EP) and 31+/-5 ppm (BA + Late EP). No changes in the boron concentration values were observed in precancerous tissue and normal pouch tissue in Early and Late EP vs BA only protocols. Measured values were within the range of 30-40 ppm and 28-38 ppm for precancerous and normal tissue, respectively. The boron concentration ratios Tumor/Precancerous tissue and Tumor/Normal tissue of the EP protocols were similar to the control without EP, in the range of 1.1 to 1.3. Conversely, the Tumor/Blood boron concentration ratio showed a decrease in tumor selectivity for both the EP protocols versus control without EP.

Conclusion: Biodistribution studies showed that Early EP induced an increase in mean gross boron concentration in tumor and would contribute to BA-BNCT-induced tumor response. Ongoing neutron autoradiography studies seek to determine if potential enhanced therapeutic efficacy would be partially due to EP induced changes in 10B microdistribution. Radiobiological studies in experimental oral cancer are necessary to assess the potential therapeutic efficacy and radiotoxicity of BA+EP/BNCT and the role of high boron concentration values in blood.
MA Garabalino and N Olaiz contributed equally

Keyword: Biodistribution, Boric Acid, Electroporation, oral cancer model, BNCT

Pa R1 04

Radiobiological in vitro and in vivo investigations on accelerator neutron source in Budker Institute of Nuclear Physics

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Introduction:
The studies were carried out using an accelerator-based epithermal neutron source constructed at the Budker Institute of Nuclear Physics in Novosibirsk Science City (Russia). The safety of neutron beam was evaluated. Neutron irradiation of U87 (glioblastoma) and FetMSC (human embryonic bone marrow) cell line was carried out. In the in vivo experiments we studied the radiobiological effects of neutron irradiation with BSH injection at a dose of 200 mg/kg intraperitoneally in immunodeficient SCID mice.

Materials and Methods:
In in vitro experiments the samples were located in a plexiglass phantom under the lithium target of the accelerator-based neutron source. The irradiation lasted 2 hours and 2 minutes with proton energy of 2.0 MeV and current integral of 2.69 mA*h. The maximum absorbed dose was 12 Gy-Eqs. The dose range was 0–12 Gy-Eqs. After irradiation, 104 cells per well were plated 96 well plates for MTT test 48 and 96 hours after irradiation. In in vivo experiments, after boron compound injection mice were irradiated with epithermal neutrons with proton energy of 2.0 MeV, and the current integral of 1.56 - 4.48 mA*h. The irradiation doses received by mice were 0-20 Gy-Eqs. Animals irradiated without boron and/or without irradiation were used as controls. We morphologically evaluated changes in the proliferative pool of the bone marrow, in the small intestine, kidneys, liver, brain, heart, and spleen.

Results:
According to the concept of tolerance of normal tissues, FetMSC, a line derived from normal embryo tissue, was more tolerant to epithermal neutron irradiation, while the response of the tumor U87 line was more prominent. Irradiation dose of 12 Gy-Eqs reduced survival fraction of U87 cells by 27% and FetMSC cells by 7%. All laboratory animals were alive 1 month after the irradiation. External pathological signs were found in mice that received doses of 16 Gy-Eqs to 20 Gy-Eqs in the form of trophic skin disorders and weight loss. The experiment shows that therapeutic dose received by mice healthy tissues during irradiation was well tolerated, and pathological structural changes in the studied tissues that have been exposed to radiation were not detected. However, at high doses of radiation, reversible changes in tissues, mostly in the small intestine and bone marrow, were revealed.

Conclusion:
Our experiments with normal or tumor cell lines irradiated with different doses suggest that effect of only neutron irradiation without boron-10 is insignificant for normal cells. Experimental data on animals show that doses up to 4 - 6 Gy-Eqs were optimal for carrying out BNCT in vivo experiments. Acknowledgments This work was funded by the Russian Science Foundation under project no. 14-32-00006 and was supported by the Budker Institute of Nuclear Physics and Novosibirsk State University.
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Keyword: bnct, radiobiological studies, accelerator

Pa B2 01

Development of a prompt gamma ray imaging detector using LaBr3(Ce) scintillator and arrayed MPPC for Boron Neutron Capture Therapy

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Introduction
In order to improve the quality of treatment of boron neutron capture therapy (BNCT), it is necessary to perform the detection of boron concentration during BNCT irradiation. In general, boron concentration has been evaluated by prompt gamma ray analysis with a high purity germanium detector and the induced coupled plasma methods. However, these procedures cannot obtain the information of the boron concentration during irradiation. The determination of boron concentration in real-time can be achieved by measuring the prompt gamma rays emitted from the reaction between boron-10 and thermal neutron. However, there are 511 keV annihilation gamma rays in BNCT irradiation fields; as a result, it is required to discriminate between prompt gamma rays of 478 keV and annihilation gamma rays. A detector system with an energy resolution below 6.5 % is required to discriminate the two gamma rays. A prompt gamma-ray imaging detector system was developed. It consists of a LaBr3(Ce) slab scintillator, 8 × 8 array Multi Pixel Photon Counter (MPPC), 64 channel amplifier, a shaper and ADCs. This paper reports the concept of this system and the results of characteristics of this system.

Materials and methods
The detector was composed of LaBr3(Ce) scintillator, 8 x 8 array MPPC, a 64 channel amplifier, a shaper and ADCs. The size of this scintillator was 50 mm x 50 mm x 10 mm. The scintillator was set up in front of the 8 x 8 array MPPC. The output of 64 MPPC channels were fed to an amplifier unit. The 64 analog outputs were digitalized by ADCs. These digital signals were stored in a PC. The bias for each channel was adjusted so that the peak position of 511 keV gamma rays matched up. A Na-22 source was used to examine the energy resolution for 511 keV gamma rays. Moreover, samples with different boron concentration, up to 5000 ppm were irradiated using the thermal neutron beam with the flux intensity of around 105 (n/cm2/s) at KUR neutron guide tube.

Results
The average energy resolution for all channels for 511 keV gamma rays was approximately 5.7 %. Two Gaussian distributions for 478 and 511 keV gamma rays were defined and the Gaussian distribution of 511 keV gamma rays overlapped the Gaussian distribution of 478 keV gamma rays. The average effect for all channels by overlapping was about 18 % in the ROI that was defined as 2σ of the Gaussian distribution of 478 keV gamma rays. It was possible to discriminate between 478 and 511 keV gamma rays by defining Gaussian distributions respectively. In addition, count rate of different boron concentrations for 478 keV gamma rays were measured and it was confirmed that it was linear. The two-dimensional distribution of 478 keV gamma rays was obtained by subtracting the effect from 511 keV gamma rays.

Conclusion
The average energy resolution for all channels for 511 keV gamma rays was about 5.7 %, which is below the required 6.5 %. Discrimination between the 478 and 511 keV gamma rays were made possible by defining two Gaussian distribution respectively. However, the Gaussian distribution of 511 keV gamma rays overlapped with the Gaussian distribution of 478 keV gamma rays; as a result, the effect from 511 keV gamma rays in the ROI was subtracted from counts of 478 keV gamma rays in the ROI. By discriminating two gamma rays, two-dimensional boron concentration distribution was obtained.

Keyword: BNCT, LaBr3(Ce) scintillator, MPPC, SPECT

Pa B2 02

Uptake of p-borono-phenylalanine by brain tumor stem cells analyzed by mass cytometry

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[Introduction] P-borono-phenylalanine (BPA) is a chemical compound used in clinical trials in boron neutron capture therapy (BNCT). BPA accumulates preferentially in the growing cells rather than in quiescent cells of the tumor. Brain tumor stem cells have been thought to be resistant to radiation and chemotherapy and one of causes of therapeutic failure. Here, we investigate whether brain tumor stem cells take up BPA using mass cytometry (Cytof). [Methods] We used brain tumor stem cells and the cells differentiated by fetal bovine serum. After exposure to BPA for 24 hours, we immune-stained them using various stem cell markers, anti-BPA and anti-CD98 (heterodimer that forms the large neutral amino acid transporter) antibody and analyzed with Cytof. [Results] In brain tumor stem cells, stem cell marker (Oct3, Nestin, Sox2, and PDGFRa) positive cells took up BPA 2 to 6 times higher than negative cells. On the other hand, in differentiated cells, stem cell marker positive cells took up BPA as same as negative cells. [Conclusion] Differentiation may lead to reduce accumulation of BPA. Effect of tumor micro-environment on BPA uptake should be considered in following experiments.

Keyword: brain tumor stem cells, p-borono-phenylalanine, mass cytometry analysis

Pa B2 03

Development of the electron tracking Compton camera for on-line imaging of 478 keV prompt gamma rays in BNCT

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Introduction: Although BNCT is known as one of the promising cancer treatment methods, we have not yet obtain good method to know the treatment effect in real time during BNCT since it is difficult to know precisely both the boron concentration and neutron flux intensity in tumor cells and healthy ones. During BNCT, 478 keV prompt gamma rays are generated by the boron neutron capture reaction. If we get images of 478 keV gamma rays and know their generation positions in real time, we can check the treatment effect. To get gamma-ray images, there have been proposed several detectors such as SPECT gamma cameras and Compton cameras. To collimate 478 keV gamma rays, a very thick collimators are needed, which causes the serious decrease of the detection efficiency and also a main reason of the noise source of gamma rays. On the other hand, a Compton camera which does not need to use thick collimator, cannot determine the incident direction of the gamma ray only as a circle due to lack of the direction of recoil electron in Compton scattering, and hence never provide a real and quantitative distributions of Boron in body. In BNCT quantitative evaluations of both boron concentration and neutron flux distribution are absolutely significant due to its strong destruction power for both tumor and normal tissue.

Materials and Methods: If we can measure the all parameters in Compton scattering by measuring the track of the Compton recoil electron, we could obtain the direction of an incident gamma ray as a point and then get proper quantitate image satisfying geometrical optics similar to optical camera.We have been developing electron-tracking Compton cameras (ETCCs) that can uniquely determine the arrival directions of sub-MeV/MeV gamma rays. It is a hybrid detector of two detectors, a Compton scatterer of the incident photon and the absorber of the scattering gamma-ray. We use a gaseous TPC as the Compton scatterer, which has a two-dimensional position sensitive gaseous detector for the detection of the track and deposit energy of a recoil electron. We also use a position sensitive scintillation camera as the absorber of scattering gamma-ray, which is set at the bottom of the TPC. We can reconstruct the arrival direction of every incident photon. Background particles such as cosmic rays and neutrons are strongly rejected by using an energy loss rate (dE/dx) in the TPC. By requiring an electron track fully contained in TPC, we can select a perfect reconstructed Compton event.

Result: Previously, we measured 478 keV prompt gamma rays generated by boron neutron capture reaction with a prototype ETCC with a 10 cm cubic TPC, and succeeded to get images of 478 keV gamma rays generated from borated polyethylene irradiated with neutrons. For the application of the real time monitoring of 478 keV prompt gamma rays during BNCT, we have developed an ETCC with a 20 cm cylindrical TPC, of which detection efficiency is about 20 times better than previous one.

Conclusion: We have developed the ETCC for the application of the real time monitoring of 478 keV prompt gamma rays during BNCT. We have a plan to measure images using an intense neutron source in this summer, and would present some results on this conference.

Keyword: BNCT, ETCC, gamma-ray imaging

Pa B2 04

Response of a CZT detector to the neutron and gamma radiation field of an accelerator based BNCT facility.

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Introduction

BNCT therapy effectivness is strongly dependent on the ability to induce a high concentration of 10B inside the neoplastic tissue. The correct evaluation of such quantity, of the boron compound spatial distribution and of the dose deposited in the tumour is a key element to further the BNCT efficacy. To such purpose a BNCT-SPECT system has been proposed. SPECT imaging of the 478 keV photon emitted in the 94% of the cases due to the 10B thermal neutron capture reaction would allow for a direct quantification of the dose delivered to the tumour. Moreover a BNCT-SPECT would be a real time, on-line imaging system, therefore it would be installed inside the treatmeant room of a BNCT clinical facility. As such it is important to study the mixed neutron and gamma background present in the treatment room during the patient irradiation and the degree to which such background interacts with the BNCT-SPECT system.

The Pavia BNCT group has studied a clinical facility based on an accelerator neutron source from a computational point of view. Moreover the clinical treatment room has been charcterized by evaluating the activation of patient, walls and air. In the present work we studied the neutron and gamma background inside the treatment room and simulated its interaction with the CdZnTe (CZT) detector that constitues our BNCT-SPECT system sensitive element. Moreover we studied the ability of the CZT detector to correctly identify the 478 keV peak due to the boron capture reaction when working in the mixed neutron and gamma background.

Materials and Methods

This study was conducted from a computational point of view using MCNP6 Monte Carlo code. At first the thermal, epithermal and fast neutron fluence was studied inside the 4x3.3x6 m3 treatment room. In a second step the gamma background present in the treatment room with and without a PMMA phantom was considered. The tissue equivalent phantom was used to evaluate the disturbante to the background radiation due to the presence of the patient during the irradiation. The main contribution to take into account was the 2.223 MeV photons emitted by the hydrogen present inside the tissue equivalent phantom. Moreover the gamma background generated by the cadmium in the CZT detector itself due to the 113Cd(n, γ)114Cd reaction was evaluated. Lastly a tumour loaded with 10B was placed inside the phatom to evaluate the 478 keV peak obtained during the irradiation of the tumour.

Results

The neutron and gamma background was evaluated in the treatment room of the Pavia accelerator based treatment facility. Then the background gamma contribution due to the tissue equivalent phantom and due to the 113Cd(n, γ)114Cd reaction inside the CZT detector were simulated. Laslty the spectrum due to the 478 keV gamma of the boron capture reaction inside the tumour was simulated and compared to the spectra due to the background showing that the detector is able to discriminate the boron peak when working in the mixed field of the treatment room.

Conclusions

The spectrometric performance of the CZT detector based BNCT-SPECT system has been simulated when the system works in the mixed neutron and gamma field typical of a BNCT treatment room. Moreover to improve the performances of the detection and imaging system it is possible to use the calculated background to create and appropriate neutron and gamma shielding.

Keyword: BNCT-SPECT, aBNCT, CZT, boron imaging

Pa B2 05

Exploring neutron autoradiography and alpha spectrometry techniques for boron measurements in bone.

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Introduction: Boron Neutron Capture Therapy (BNCT) is being studied as a potential treatment for osteosarcoma disease. The evaluation of the absorbed dose requires knowing boron concentration in the irradiated tissues. Neutron autoradiography and alpha spectrometry techniques have proved to be reliable for the boron quantification in soft tissue samples. However, in the case of hard tissue samples, it is necessary to follow new extended protocols that overcome the limitations related to the preparation of thin tissue sections. Approaches introduced in previous works were tested in several bone samples and compared with computational simulations that reinforce the understanding of both techniques.

Materials and Methods: Extended protocols for neutron autoradiography and alpha spectrometry of hard tissues proposed in previous works require samples with thickness of ~100 microns. Biopsies of bone with cross section of about 1 cm2 were abraded with a rotary diamond saw in order to achieve the desired thickness. Two kinds of samples were studied. Femur samples from a biodistribution experiment in sheep treated with BPA and a set of hard tissue samples containing boron from undetermined origin. The samples analyzed by the autoradiography technique were irradiated at the RA-3 reactor (Argentina). Tracks imprinted in Lexan by the effect of neutron capture were revealed by chemical etching and counted with an image processing software. In addition, stochastic simulations were performed and compared with the experimental calibration curve as a reliability test. The alpha spectrometry measurements were performed at the TRIGA Mark II reactor of Pavia University (Italy). Boron concentration was determined from the experimental spectra using the stopping power of alpha particles in bone samples. This quantity was assessed with dedicated simulations using the experimental measurement of bone elemental composition by PIXE technique. The resulting spectra were reconstructed by MCNPX simulation and analytical calculation to gain a deeper insight into the measurement process. Both methods were compared with ICP-OES measurements.

Results: For the samples of sheep femur the studied techniques are in agreement, showing a mean 10-boron concentration of about 8 ppm. Regarding the samples containing boron from unknown source, ICP measurements show higher boron concentrations than what measured with spectrometry and autoradiography. Indeed, ICP is not able to distinguish the different boron isotopes. However, alpha spectrometry and autoradiography, both detecting only 10-boron, are in good agreement. A remarkable overlap between the autoradiography calibration curve and the stochastic simulation was observed. The two computational methods explored to reconstruct the alpha spectrometry spectra for different samples demonstrated that the procedure employed to determine boron concentration is reliable and robust.

Conclusions: The extended techniques are capable to measure 10-boron concentration in hard tissues with an acceptable accuracy (Error<15%). Both methods have been used to study the biodistribution of boron in hard tissues improving the dose evaluation in potential osteosarcoma clinical cases and also to evaluate dose absorbed by normal bones involved in BNCT irradiation. This is important, since the experimental results demonstrate that bone behaves as other normal tissues, at least when BPA is administered. Normal bone could be thus a limiting tissue when calculating treatment plan. Simulations were employed to corroborate the proposed techniques, demonstrating that the results obtained are robust and that the methods are a valid option to measure boron concentration in bone.

Keyword: Alpha spectrometry, neutro autoradiography, osteosarcoma, bone

Pa P3 01

Development of real-time neutron detector for beam quality discrimination measurement using LiCAF scintillator and neutron moderator

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"Introduction"
The epithermal neutron beam has been used in Boron Neutron Capture Therapy (BNCT) in order to treat deeper region of human body. However, besides epithermal neutrons, fast neutrons, and gamma rays are mixed in this neutron beam. In BNCT, localized irradiation is performed using a collimator, there is a possibility that these fast neutrons and gam-

ma rays passed through the collimator or scattered by the irradiation room wall and bed are irradiated outside the irradiation field. Conventionally, gamma ray doses have been evaluated using a thermoluminescence dosimeter, and thermal neutron fluence has been evaluated using a gold foil activation method for several evaluation points in whole body. However, these two evaluation methods are performed after irradiation. Furthermore, it is difficult to evaluate the contribution of epithermal and fast neutrons with different beam quality, because the beam quality of the neutron energy spectrum differs at different body regions.The purpose of this study is to develop a real-time neutron detector capable of performing beam quality discrimination measurement under the mixed field of these various radiation components.

“Materials and Methods”
The combination with small LiCAF scintillator and quartz fiber was used in this study as thermal neutron detector. Because LiCAF scintillator was not able to directly detect the epithermal and fast neutrons, the optimization of moderator thickness was performed. Two layer spherical moderators with different materials were optimized to have selective sensitivity to the epithermal or fast neutrons.
The Monte Carlo code PHITS was used to optimize each moderator. The neutron energy spectrum at each body region was calculated using a humanoid water phantom under a typical BNCT irradiation for brain tumor. Reaction rate of 6Li(n, α)T was calculated with two layer spherical moderators composed of polyethylene and polyethylene loaded with Lithium fluoride. The sensitivity of the detector to epithermal neutrons was evaluated by changing the material type and thickness of the moderator.

“Results”
It was confirmed that the neutron energy spectrum at each position was different. The thickness of the moderator was optimized to the epithermal neutrons for each neutron energy spectrum.

”Conclusion”
We confirmed that the combination with LiCAF scintillator and optimized moderator were able to detect epithermal neutrons. The optimization of moderator for fast neutrons will be performed.
Detector characterization will be performed by preparing an optimized moderator using a 3D printer and setting detectors for thermal, epithermal and fast neutrons at each position of the humanoid water phantom using a neutron beam at KUR (Kyoto University Reactor). Finally, we have a plan to do dose evaluation for each position using developed neutron detectors.

Keyword: neutron detector, real-time, LiCAF, moderator

Pa P3 02

Design of a BNCT irradiation room based on proton accelerator and Be target

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The future BNCT treatments will be carried out with proton accelerators, more adequate for healthcare environments. The Italian National Institute of Nuclear Physics (INFN) manufactured a Radio-Frequency Quadrupole accelerator delivering a 5MeV, 30mA proton beam. Coupled with a beryllium target, it can produce a high neutron flux through the reaction 9Be(p, n)9B, and with an appropriate Beam Shaping Assembly (BSA) can provide an epithermal neutron beam suitable for the treatment of deep-seated tumors. In the present work, some radiation protection issues for a clinical irradiation room based on this technology are investigated. The BSA activation was studied experimentally and with Monte Carlo simulations. The activation of air, patient and walls in the room was evaluated. Absorbed dose, equivalent dose and ambient dose equivalent were calculated in the room air, and doses absorbed by patient principal organs were evaluated. The environment conditions were optimized by testing different walls composition based on these dosimetric calculations.
Experiments were conducted at the research nuclear reactor TRIGA Mark II of Pavia University. Samples of AlF3 (aluminum fluoride, principal BSA constituent) were studied through Neutron Activation Analysis. The geometry of BSA with the evaluated composition was reproduced with MCNP6 code, and a simulation with coupled neutron-photon transport was run to estimate the BSA residual activity after a 2 hours clinical irradiation. A model of a treatment room, with appropriate dimensions regarding patient positioning and doses outside, was also simulated. Since the neutron flux in the room is about 10^9 cm-2s-1, the walls and air activation is an important concern. Argon is a noble gas naturally present in air in percentages around 0.9%, its activation produces the radioisotope Ar-41. The air activity due to irradiation was simulated with different walls compositions: ordinary concrete, concrete enriched with 5% of natural boron, ordinary polyethylene and polyethylene with 7% of natural lithium. The effect of these materials on the absorbed dose, equivalent dose and ambient dose equivalent distributions in the room was investigated. An anthropomorphic geometrical model (MIRD phantom) was implemented in the

room in a representative position for patient treatment. This allowed the evaluation of the doses absorbed in the principal organs and the dependence of these quantities on the walls composition. Urine activation and overall patient activation were also calculated.
Trace elements in AlF3 powders were quantified, allowing the evaluation of BSA activation due to a typical treatment time. Activation and dosimetric characterization of the BSA designed for the treatment of deep-seated tumors was thus carried out. The calculated activation of air and walls showed that the best scenario for a clinical irradiation room is the one with borated concrete walls. This result is confirmed when considering dosimetric quantities in the room and patient activation.
Borated concrete was proven the best choice for the walls, concerning activation and dosimetric quantities, because it ensures an advantageous reduction of thermal flux in the room. Lithiated polyethylene leads to similar results, however concrete is more efficient in gamma shielding, and its enrichment with boron is easier to obtain. This work confirms the feasibility of the construction of a BNCT irradiation room with the neutron source based on (p, n) reaction in beryllium, coupled with a BSA of aluminum fluoride. This work also provided a valuable feedback for the tailoring of the epithermal neutron beam, demonstrating that the performance evaluation cannot be based only on physical beam parameters or dose distribution in the tumor, but must also take into account peripheral dose and environment considerations. Further studies are ongoing to evaluate the effects of B-10 in walls concerning the development of a SPECT system for on-line dose monitoring.

Keyword: accelerator-based BNCT, radiation protection, neutron activation

Pa P3 03

Comparison of relative biological effectiveness (RBE) doses and the photon iso-effective dose model for predicting the normal tissue complication probability in boron neutron capture therapy (BNCT) of head and neck cancer patients

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Introduction
In boron neutron capture therapy (BNCT) the biological dose is conventionally calculated as a sum of four dose components after multiplying each absorbed dose component with a constant RBE factor or a (boron) compound biological effectiveness (CBE) factor. Fixed RBE and CBE factors are applied, although they depend on the cumulative irradiation time as well as the end point used, the cell type, and the dose given per fraction, and thus should be derived for each irradiation condition individually. An alternative biological dose calculation method, the photon iso-effective dose formalism, has been proposed for BNCT to replace the RBE factor-based dose calculation. The model takes into account the dose rate and the cumulative dose per fraction using the first-order repair of sublethal lesions in the modified linear-quadratic model, and considers synergistic interactions between low-LET and high-LET radiation. The formalism was recently extended, defining the photon iso-effective dose as the dose that produces the same tumor control rate or the normal tissue complication rate as a given combination of the absorbed dose components of BNCT. In L-boronophenylalanine (BPA)-mediated BNCT for head and neck (HN) cancer, the highest normal tissue doses are often accumulated in the buccal mucosa as the mucosal membranes take up BPA approximately twice as much as what is present in the blood at the time of neutron irradiation. In addition, the mucosal membranes are radiosensitive (CBE=2.5). Thus, the mucosal membrane absorbed dose is often the dose-limiting factor.

Materials and Methods
The extended photon iso-effective dose formalism was applied to calculate the normal tissue complication probability (NTCP) for the mucosal membranes for patients with recurrent HN carcinoma, who were treated with BNCT in a phase I/II clinical trial in Finland in 2003 to 2011. The complication probabilities were compared to those obtained based on the traditional RBE doses. The NTCP calculated based on the maximum mucosal membrane dose was compared with the observed mucositis at 4 to 5 weeks after the 1st BNCT. The parameters for the photon iso-effective dose calculation were derived from the in vivo animal model data and the patient data.

Results
Grade 3 mucositis was observed in 8 (27%) out of the 30 patients studied after 1st BNCT. The maximum absorbed physical dose to the mucosal membranes was 3–6 Gy, which corresponds to RBE doses of 8-14 Gy(W), predicting ≥grade 3 mucositis only for 0.03 out of 30 patients. The photon iso-effective doses were 12-18 Gy(IsoE) predicting ≥grade 3 mucositis for 7 (23%) of the 30 patients. A binary logistic regression analysis showed

that the iso-effective doses were associated with observed grade 3 mucositis (p=0.018), whereas the physical absorbed doses or the RBE doses were not (p=0.801 and p=0.085, respectively).

Conclusions
The result suggests that the photon iso-effective dose model predicts mucosal membrane toxicity after BNCT more reliably than the traditional RBE model or the physical absorbed doses. Evaluation of mucosal toxicity in a larger patient series is warranted to verify the findings.

Keyword: Mucositis, RBE dose, isoeffective dose, head and neck cancer, bnct

Pa P3 04

On the upper limit for the energy of epithermal neutrons for BNCT

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Introduction
At present, the recommendation from the IAEA limits the contribution of the fast neutrons. The energy used to define the separation between epithermal and fast neutrons was set to 10 keV. This value is regarded as quite arbitrary, as it was chosen for reactor-based BNCT to avoid large fluxes of neutrons with energies up to the MeV range. Since the new accelerator-based neutron sources for BNCT yield a significant proportion of neutrons near 10 keV, this is relevant in the design and optimization of such equipment.

Materials and Methods
Computational simulations have been performed using MCNPX. The analysis has taken into account relevant Figures of Merit (FOM). Several different tissues have been considered.

Results
Our results suggest that neutrons with an energy near and above the 10 keV limit could be usable for BNCT treatments. That value reaches 17 keV for the standard ICRU4 tissue. Some new light is given to this issue.

Conclusion
The current recommendations should be reviewed either to change the limit or to establish new FOM to determine the optimum features for the neutron sources.

Keyword: epithermal neutrons, fast neutrons, IAEA recommendations, Monte Carlo simulations

Pa P3 05

Computational assessment of BNCT neutron beams using radiobiological models

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Introduction: Novel computational tools and innovative analysis criteria were developed to assist treatment planning procedures and assess BNCT beam designs in a realistic clinical context. Based on radiobiological figures of merit such as Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) models, the proposed workflow suggests a complementary strategy to the standard procedures for evaluating the safety and therapeutic potential of a neutron beam.

Materials and Methods: TCP models that take into account inhomogeneous dose distributions were developed for photons and for mixed field of BNCT radiation. These models, jointly with a NTCP model, were applied to assess and compare neutron beams in a realistic clinical scenario. An upgrade of the Argentine reactor RA-6 neutron beam was tested under the proposed criteria. The upgraded neutron beam was designed to improve the therapeutic effect of BNCT on large and deep tumors such as those that occur in head and neck (HN) cancer. The performance of the new design was assessed in light of a retrospective evaluation of the clinical-veterinary BNCT treatments carried out in dogs with the actual mixed thermal-epithermal beam of the RA-6, and in HN cancer patients treated

with the epithermal beam FIR1 in Finland. Two criteria for the irradiation time calculation were explored: CRITERION#1, to equate the maximum absorbed doses in mucosa delivered per BNCT application in the current treatment, and CRITERION#2, to equate the NTCP values of the current treatment.

Results: The resulting probabilities of tumor control and normal complication for the delivered treatments are in line with the observed clinical outcomes. Although these results are not conclusive about the predictive power of the proposed models, they help to sustain the suitability of the figures of merit. The evaluation of these radiobiological figures of merit for the new RA6 beam design shows that, regardless of the criterion followed to compute irradiation times, potential benefits could be achieved in the dog treatments. In cases of head and neck cancer patients, the therapeutic potential of RA-6 new design could be unfairly underrated by the fact that the gamma contribution is significantly higher than that of the FIR1 reference beam. Using the proposed tools, it can be confirmed that in the studied cases and despite the unwanted low LET radiation component, RA-6 can achieve treatments comparable to FIR1 in terms of tumor control and patient safety.

Conclusions: An adequate performance assessment of the new beam design within a clinical scenario and its comparison with another BNCT beam with different spectral characteristics required the implementation of appropriate figures of merit and innovative analysis criteria. Complementing the analysis of the physical characteristics of the beam designs, the proposed workflow has proven that it is capable of asses BNCT beams in terms of the potential therapeutic outcome.

Keyword: TCP, NTCP, Neutron Beam Assessment, Iso Effective Doses

Pa P3 06

How do photon iso-effective tumor doses derived from in-vitro BNCT studies compare to those from in-vivo cancer model data?

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Introduction

The comparison of Boron Neutron Capture Therapy with photon radiation therapies requires a model for dose calculations that predicts an adequate "photon-equivalent" value. We reported that the standard model of dose calculation in BNCT, that uses fixed RBE/CBE factors, leads to unrealistically high RBE-weighted tumor doses. We then introduced a more suitable approach 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 in BNCT. Our formalism with radiobiological parameters derived from the human melanoma metastatic cell line Mel-J was applied to reevaluate the dosimetry of the Argentine cutaneous melanoma BNCT trial. Results showed that standard approach was unsuitable to explain the observed outcome, while the number of controlled tumors predicted by the new formalism was statistically consistent with the observed values.
Recently, we extended the formalism redefining the photon iso-effective dose as the reference dose that produces the same "tumor control" as a given combination of doses in BNCT. This model with parameters derived from the hamster cheek pouch in-vivo oral cancer model was applied retrospectively to evaluate the dosimetry for head and neck (HN) cancer patients. Results showed that RBE-weighted tumor doses were unable to predict the clinical outcome while predictions based on the proposed model were compatible with the observed response.
A very important question that arises is whether or not the nature of the experimental data used to determine the parameters of the photon iso-effective model (i.e., in-vitro vs. in-vivo data) affects the consistency of the results. In this work, we address this question by introducing the photon iso-effective dose model for HN tumors based on in-vitro survival data for a primary human cell line, and by comparing doses and predictions of the model based on both in-vivo and in-vitro data in HN cancer patients treated with BNCT.

Materials & Methods

The survival of the UTSCC16A primary human cell line was determined as a function of

the dose for photon irradiations, and for neutron irradiations alone and in the presence of the BPA. Neutron irradiations were carried out in the Thermal Column of the TRIGA reactor at Pavia University, and photon irradiations using a 6MV LINAC at S. Matteo Polyclinic Foundation (Pavia). We used the experimental data to determine the radiobiological parameters of the modified linear-quadratic survival models for the reference radiation (α_ref, β_ref) and for BNCT (α_n, β_n, α_B, β_B) (González et al., 2015). The obtained parameters were applied to calculate photon iso-effective doses in HN cancer patients treated in Finland. Dose-volume histograms for tumor were compared to those obtained using the parameters from in-vivo BNCT studies. The observed outcomes in patients were analyzed in light of the RBE-weighted and photon iso-effective doses.

Results

Photon iso-effective doses obtained with the in-vitro radiobiological parameters for the analyzed patients are 7% to 46% lower than the RBE-weighted tumor doses. These results reinforce our previous assertions that RBE-weighted tumor doses often overestimate the real photon-equivalent values. In addition, in-vitro and in-vivo data-based dose estimations show agreement with differences less than 5%. Finally, the most likely value of controlled tumors coincides with the observed result only for photon iso-effective doses.

Conclusion

Regardless the nature of the experimental data used to determine the parameters of the dose model, photon iso-effective doses are considerably lower than the standard RBE-weighted tumor doses. Further studies are ongoing to conclude that the in-vivo and in-vitro data-based photon iso-effective dose models for HN tumors are in agreement.

Keyword: photon iso-effective dose, in-vivo oral cancer model, in-vitro cell survival

Pa P3 07

Extension of the photon iso-ffective dose model to the dose-limiting normal tissues for BNCT of head and neck cancer

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Introduction

We have introduced a new model for the calculation of dose delivered by BNCT that essentially translates BNCT doses into photon doses with the same effect on cancer without using fixed RBE/CBE factors. We now present an extension of this model, introducing the photon iso-effective dose as the reference dose that produces the same effect as a given combination of the dose components in BNCT not only for tumors (where the effect is tumor control) but also for dose-limiting normal tissues. This extension requires the inclusion of dose-response assessments in in-vivo cancer models and suitable expressions of the normal tissue complication and tumor control probabilities for photons and for the mixed field BNCT radiation.

The acute effect of main concern is oral mucositis grade 3 or higher (G3+) when treating head and neck (HN) cancer patients with radiation. We present here a photon iso-effective dose model developed for the calculation of doses in the mucosal membranes. The proposed model with parameters derived from both animal BNCT studies and human photon radiotherapy data is applied to evaluate photon iso-effective doses in the clinic for HN cancer. We discuss the suitability of the dose model in the light of the obtained results.

Materials & Methods

Let D1, …, D4 be the absorbed dose components in BNCT. Let D_ref be the dose of the photon reference radiation. The photon iso-effective dose is defined as the photon dose D_ref=D_ref(D1, …, D4) that produces the same normal tissue complication probability (NTCP) as the combination of absorbed doses in BNCT. Then, Dref=Dref(D1, …, D4) is the dose that satisfies

NTCP_ref(D_ref)=NTCP_BNCT(D1, …, D4).

Strigari et al. (2012) proposed a NTCP model that predicts G3 or higher mucositis after HN cancer radiotherapy with photons for standard schedules of dose delivery. This model assumes the validity of the concept of the equivalent total dose in 2-Gy fractions. Then,

the NTCP_ref is obtained rewriting Strigari's model in terms of the single-fraction dose D_ref.
Aiming to get equal effects, the photon iso-effective dose D_ref for mucosa in BNCT must satisfy
-ln(S_ref(D_ref))=-ln(S_BNCT(D1, …, D4)).

Results
Closed formulas for the photon iso-effective doses and for the NTCP corresponding to a dose combination D1, …, D4 were obtained.
The dosimetry in the mucosa for the analyzed clinical studies reveal that photon iso-effective doses are higher than the corresponding RBE-weighted values. The NTCP values computed using the iso-effective doses for the dogs show that the probability of G3+ mucositis after BNCT is very low (<0.001), which is in line with the clinical outcome. The corresponding values for humans show that the predicted number of patients that would develop G3+ mucositis is compatible with the clinical outcome. However, when RBE-weighted doses were used the predicted number is unacceptably low.

Conclusion
The extension of the photon iso-effective dose model, which includes information from dose-response assessments in animal models and humans has, for the first time, allowed the determination of photon iso-effective doses for severe mucositis resulting from BNCT for HN cancer.

Keyword: photon iso-effective dose, NTCP, head and neck cancer

Pa P3 08

Development of Real-Time BNCT Neutron Beam Monitor Using Thin Silicon Sensor

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Introduction
BNCT facilities have been constructed at several hospitals in Japan. One of importance for BNCT is the neutron beam measurement. Real-time measurements of neutron fluxes are preferred for the facilities while off-line neutron measurements have been performed using neutron activation techniques of gold foils and fibers. In this study, we have developed new real-time neutron detectors able to measure BNCT neutron beam, directly.

Materials and Methods
The new real-time BNCT neutron monitor has been developed using a pn diode. The diode has a thin silicon volume of 30 to 60 micron in thickness. This diode can measure gamma rays under 480 mGy/h irradiation. This is a big advantage of neutron measurements under high gamma-ray fluxes coexisting in the BNCT beams. To detect large intensity neutron beam, ultrathin LiF evaporated on a plate is attached on the diode. In the neutron measurements, tritons produced by the Li6(n, t)He4 reaction were detected at the pn diode.
Specification of our neutron detector have been experimentally obtained at KURRI-BNCT beams, in Kyoto University Research Reactor Institute, Osaka, Japan. The neutron detector was placed at the neutron therapy position and was irradiated with the thermal neutron beams, up to 1x10^9 (n/cm^2/s).

Results
The real-time measurement of neutron beam intensities were successfully performed at the KURRI-BNCT. Clear neutron peak, which is separated from gamma-ray component, is observed. Good linearity of the neutron count rates on the neutron fluxes are obtained. Our neutron detector can measure the direct BNCT neutron beam in real time.

Conclusion
The neutron detector based on the thin pn diode can measure the direct BNCT neutron beam in real time. We hope our neutron detector will be applied to the BNCT neutron beam monitors.

Keyword: Real-time measurements, silicon detector, KURRI-BNCT

Parallel Session

Pa Cl2 01

Boron neutron capture therapy for vulvar melanoma and extramammary Paget's disease of the genital regions

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Introduction: The most commonly recommended treatment for melanoma and extramammary Paget's disease (EMPD) of the genital region is wide surgical excision of the lesion. However, this is highly invasive and it can lead to a variety of functional and sexual problems. Alternative treatment modalities have been enployed for local control when wide local excision was not feasible. In the present report we describe four patients with genital malignancies who were treated by means of boron neutron capture therapy (BNCT).

Patients and Methods: One patient had a vulvar melanoma (VM) and three had EMPD of the genital region. BNCT was carried out at the Kyoto University Research Reactor between 2005 and 2014 using para-boronophenylalanine (BPA) as the boron delivery agent. The patients were irradiated with an epithermal neutron beam between the curative tumor dose and the tolerance skin/mucosa doses. Tumor responses were graded as follows: complete regression (CR), complete disappearance and regression of pigment plaque and tumor by visual inspection, CT scan or MRI; and non-CR, no regression or incomplete regression of plaque and tumor. Complication of normal skin/mucosa and pain was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. We evaluated the local response every three months after the therapy. A survival analysis was made in October 2017.

Results: All lesions regressed completely with depigmentation within six months. There were no local recurrences in the radiation field during follow-up ranging from 1.1 to 6.9 years.

(1) VM (Case 1)

A 73-year-old woman presented with a black macule on her vulva. A small nodular lesion (1.5 cm) was resected for histopathological examination at the referring hospital and it was diagnosed as a lentiginous mucosal melanoma. At the time of BNCT, the 2.5×4.5 cm flat lesion was asymmetrical in shape and variable in color and had not invaded the vaginal mucosa. There was no evidence of brain, chest, or abdominal metastases. Epithermal neutrons were administered over 49 minutes at a maximum dose of 8.0 Gy-Eq to the normal mucosa and at a minimum dose of 29 Gy-Eq to the melanoma. Subsequently she developed slight vulvar swelling and pain after irradiation, but these symptoms resolved almost completely within one month. The black macule slowly faded and was no longer visible four months later. There were no severe local adverse events such as ulceration. Although she died of disseminated melanoma 1.1 years later, there was no local recurrence.

(2) EMPD (Cases 2, 3 and 4)

The three patients with EMPD showed similar responses in tumor and normal tissue after BNCT. All of them achieved CR within 6 months and the most severe adverse event in normal tissue was moderate skin erosion during the first two months, which was subsequently resolved with a skin medication. Dysuria or contact pain persisted for two months and gradually diminished thereafter, and resolved completely within four months. One patient died of heart disease at 3.2 years following treatment with no recurrence, whereas the remaining two patients were still alive and without evidence of local or regional recurrences 6.5 and 6.9 years following BNCT.

Conclusions: This is the first clinical report of treatment of patients with VM and EMPD by BNCT, which resulted in complete local tumor control. Our results suggest that BNCT may be a promising treatment modality for VM and EMPD that heretofore have been considered radio and chemotherapeutically resistant tumors.

Keyword: BNCT, malignancies of the genital regions, clinical results

Pa Cl2 02

Reporting BNCT: A new approach towards an international standard

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The appearance of accelerator-based neutron sources for BNCT in hospitals will lead to an increase of such facilities around the world. In order to be able compare and repeat results, an internationally accepted reporting system will be mandatory. Up to now, a number of models for prescribing dose have been developed on a local level for single sites. Efforts to develop an international standard for reporting dose in BNCT have been made but its implementation was not successful [1, 2].
The absorbed dose as a macroscopic quantity is the basic parameter for prescribing, recording and reporting a procedure in conventional radiotherapy, where the microscopic dose distribution of short range high-LET particles is averaged over macroscopic volumes. In BNCT, non-stochastic "single hit effects" have to be taken into account and therefore the absorbed dose concept is not suitable to predict expected effects and hence is not a good solution for reporting. Furthermore, in BNCT several dose components with different biological impact have to be considered. In the past, it was suggested to report the different dose components separately [1, 2] leading to a complex system of numbers, which were difficult to handle and therefore were not very much appreciated.
A standardized terminology has to be mathematically correct and in agreement with international rules for terms and their units (Le Système International d'Unités, SI). The terms used have to be unequivocal, as short as possible and indicate the most important features of quantity. From a clinician's point of view, the numbers reported should allow to predict a clinical outcome.
We will demonstrate that Φ (the thermal neutron fluence integrated over the irradiation time T) together with the concentration of 10B in blood might be the most important parameters for reporting. They are independent from any model used for prescribing at a given facility. If these parameters are reported, together with the amount of fast neutrons and gamma rays emitted by the source, they could then be used as input parameters for treatment planning systems at other facilities, in order to obtain a good estimation for understanding and reproducing results obtained elswhere. We hope that our suggestion will contribute to the discussion for developing an international standard for reporting BNCT.
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Keyword: standardisation, reporting dose, reporting BNCT, prescribing BNCT

Pa Cl2 03

Boron neutron capture therapy for malignant pleural mesothelioma: A case report

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[Introduction]: In the treatment of malignant pleural mesothelioma (MPM) with BNCT using two anterior-posterior ports, the large dose gradient exists between the tumors in the lateral and mediastinal sides. In our previous clinical study on BNCT for MPM, the small number of patients survived for the period longer than three months. In the longer-survived patients, the lateral-sided tumors shrunk or remained stable in size. In this article, we reported the treatment of the patients suffering from large MPM tumors spreading between the lateral and dorsal skin and pleura.

[Patient]: A 64 year-old man with MPM had received a number of chemotherapy cycles. His main symptom was stiffness of the neck and back. The large MPM tumors refractory to the chemotherapy located mainly between the dorsal and lateral skin of the thorax and the pleura rather than between the pleura and the lung parenchyma. He referred to our center for further treatment of MPM with BNCT. Since the tumor was so large that the epithermal neutron beam using the maximum-sized collimator could not encompass all the volume of the tumor, the BNCT was carried out in order to alleviate the symptom.

[Results]: The BNCT for the large MPM tumors mainly located between the dorsal and lateral skin of the thorax and the pleura was performed with an epithermal neutron beam using a 24 x 24 cm square collimator. The irradiation time, 20 minutes, was determined according to the dose constraint for the skin. Dose constraint was set to 9.0 Gy-Eq as a maximum dose for the skin. The dose delivered to the tumors ranged from 0.1 to 58 Gy-eq. Since approximately one third of the whole tumor volume existed out of the collima-

tor, the tumor volume greater than 50 % of the tumor received less than 20 Gy-eq. However, the tumor volume greater than 1, 500 cm3 was irradiated with the dose greater than 20 Gy-eq. The maximum dose delivered to the liver, left lung and spinal cord was 4.6 Gy-eq, 7.5 Gy-eq and 1.9 Gy-eq, respectively. The mean left lung dose was 2.8 Gy-eq. For two month after BNCT, no acute adverse event greater than grade 3was experienced. At two months after BNCT, a grade 2 lymphopenia developed. The computed tomography (CT) examined at one month after BNCT, the tumor size remained stable in size.

[Conclusion]: No sever acute adverse event was observed in the treatment of large MPM tumor with BNCT.

Keyword: malignant pleural mesothelioma, BNCT

Pa Cl2 04

Boron Neutron Capture Therapy for High-Grade Gliomas –Consolidating Published Evidence in One Place

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Introduction: High-Grade Gliomas are a depressing disease to treat. Despite the best combined modality therapy, survival is still dismal. Boron Neutron Capture Therapy (BNCT) is a next-generation targeted charged particle radiotherapy that can deliver high dose of radiation to tumour cells while sparing normal tissues. Numerous studies have been published over the years, and this report is an attempt to consolidate the safety and efficacy of BNCT of all these studies in the treatment of High-Grade Gliomas.

Materials and Methods: BNCT studies of patients with High-Grade Gliomas were identified using a search through PUBMED databases. Differences in the methodologies and outcomes of the studies are explored. The consolidated results of efficacy and safety were compared against a phase III trial where similar patients were treated with the standard therapy base on the Stupp Protocol, consisting of external beam radiotherapy with oral temozolamide.

Results: From all the published studies, a total of over 500 patients with GBM have been treated with BNCT. BNCT is associated with median overall survival that is comparable, if not superior to standard therapy. However, interpreting the results from the various studies was challenging due to marked variabilities in terms of methodology across them.

Conclusion: Compared to the current best systemic therapy, BNCT is just as efficacious as standard therapy. We hope that the consolidated results presented here makes it easier for the BNCT community to promote BNCT with those not familiar with BNCT. We also hope that the international BNCT community will work together to standardise reporting of results.

Keyword: Glioblastoma Multiforme, Anaplastic Astrocytoma, High Grade Glioma, Boron Neutron Capture Therapy

Pa Cl2 05

First Patient from Singapore to Receive Boron Neutron Capture Therapy - Challenges Met and Lessons Learnt

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Singapore is a small country in South East Asia with no facilities for Boron Neutron Capture Therapy (BNCT). As such, patients who desire BNCT are requried to travel overseas for it. In 2018, an 8-year-old boy became the first known patient from Singapore to receive BNCT.
His treatment journey was however one with lots of ups and downs, not just from the medical point of view, but equally importantly from the psychosocial point of view. Some of the issues faced were not expected.
We describe the journey taken by him, his family and the healthcare team that took care of him. This is in order to highlight the various challenges encountered and how they were overcomed, leading to lessons learnt and experienced gained in the process.

Keyword: Boron Neutron Capture Therapy, Medical Tourism, Challenges

Pa Cl2 06

Dosimetric Comparison of Boron Neutron Capture Therapy, Proton Therapy and IG-IMRT for Recurrent Anaplastic Meningioma

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Introduction: A 54-year-old male with anaplastic meningioma that has recurred two after two surgeries and two courses of external beam radiotherapy sought further treatment for his lastest recurrence. The options considered were Boron Neutron Capture Therapy (BNCT), Proton Therapy and Image Guided- Intensity Modulated Radiotherapy (IG-IMRT).

Materials and Methods: Three treatment plans were generated for each of the treatment modalities. They were subsequently compared with respect to dose coverage by the tumour and dose received by the organs-at-risk.
Results: Comparing the plans for all three treatment modalities was a challenge as each treatment modality each has its own perculiarities when it comes to plan evaluation. The final analysis of the comparison will be reported at the conference.

Conclusion: In a heavily pre-irradiated location, re-irradiation to achieve tumouricidal dose is a difficult task with any of these advanced technologies. This exercise illustrates that we should take a step back at times to look at whether the patient needs to be treated, and not just how the patient should be treated. It also ilustrates the difficulty in comparing different treatment modalities.

Keyword: Boron Neutron Capture Therapy, Proton Therapy, Image Guided Radiotherapy, Meningioma

Pa Cl2 07

B-10 concentration kinetics in the tumor and blood in patients administered with BPA: a critical review

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Introduction:
B-10 concentration kinetics in the tumor and normal tissues are indispensable for BNCT dose planning. However, direct measurements of the kinetics before BNCT for each patient is rather difficult. Therefore, knowledge of the kinetics obtained from many patients is quite important for predicting B-10 concentration during neutron irradiation.

Method:
By using literatures including the author's reports, we analyzed and summarized B-10 concentration kinetics in the tumor and blood in patients administered with BPA.

Results and Discussion:
There were a few reports describing measured B-10 concentration kinetics in patients. In addition, administered dose of BPA varied largely and ranged from 100 to 500mg/kg body weight. Duration of BPA infusion also varied from 1 hour to 5 hours. The differences caused large variation in peak B-10 value and decrease kinetics after the end of BPA infusion. However, the variations became smaller when the B-10 values were normalized to the peak values. There was a tendency that rapid infusion time yields rapid clearance of B-10 from the blood after the end of BPA infusion. Absolute tumor B-10 concentration and tumor-to-blood ratios varied according to dosage of BPA and duration of infusion. Mean tumor-to-blood ratios ranged from 1.4 to 2.6 by 100mg/kg BPA(argentine) or, 3.4±0.83 by 200mg/kg BPA(Japan), for malignant melanoma, 1.9 to 2.6 by 130-250mg/kg BPA (USA) and 3.1 to 4.7 by 290-450 mg/kg BPA (Finland, based on calculation model) for glioblastoma. Recently, Japanese group adopted continuous infusion method with decreased infusion speed during neutron irradiation. This method yielded relatively constant blood B-10 values during neutron irradiation. However, they did not measure B-10 concentration either in the tumor or normal tissues under this continuous infusion with decreased speed. They assumed that the infusion method might yield the same tumor-to-blood and tumor-to-skin ratios as those by after the stop of BPA infusion.

Conclusion:
In actual BNCT, uncertainty in B-10 concentration kinetics for each patient is inevitable. Consequently, even we make radiation dose planning based on the averaged kinetics of BPA described here, the planning should have enough safety dose margin for normal tissues. If we want to realize more accuracy in dose planning, direct measurement of blood B-10 concentration during neutron irradiation might be helpful, if possible. The measured values can be used to calibrate pre-determined dose.

Keyword: BPA, B-10 concentration kinetics, blood, tumor

Pa Cl2 08

How much does tumor location affect the treatment field size passively determined by a dose constraint to the mucosa in head and neck boron neutron capture therapy?

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Introduction: In performing boron neutron capture therapy (BNCT), there are some limitations of treatment application due to the short range of thermal and epithermal neutron that restricts beam settings and patient setup condition. Especially in head and neck cancer (HNC) cases, a prescribed dose is often passively determined by a dose constraint to the mucosa that is recognized to be sensitive to BNCT. Furthermore, because of the complicated mucosal structure and the inhomogeneous distribution of neutron flux in tissues, it is difficult for general oncologists to immediately estimate how much prescribed dose is achieved and easily judge a treatment indication for each case in advance of a consultation to the specialist for BNCT. In this study, we examined the relationship between tumor location and treatment indication based on tumor dose in BNCT for HNC. Especially, as a dose distribution for the biological photon-equivalent dose (Gy-Eq) is shaped into an ellipsoid in parallel to skin and the distribution to depth direction from skin is more limited compared to the other direction, this study focused on the dose distribution of depth direction from skin.

Materials and methods: Fourteen HNC patients with a lesion at the orbita, parotid gland, nasal cavity, maxillary sinus, nasopharynx, maxilla, mouth (maxillary gingiva, buccal mucosa, tongue, or floor of mouth), oropharynx (tongue base), hypopharynx, glottis, or left level II cervical lymph node, who underwent radiotherapy in our hospital, were enrolled in this analysis. BNCT treatment planning was performed using a past planning CT image dataset for each case. Treatment planning was performed using Simulation Environment for Radiotherapy Applications (SERA), and optimization of beam alignment and dose calculation were performed with considering patient setup after delineation. For calculation of photon-equivalent dose, the values of tissue/blood ratio of the boron atom (T/B) and compound biological effectiveness (CBE) factor were assumed 1.0 and 4.9 for mucosa and 3.5 and 4.0 for tumor with a blood boron concentration of 25 ppm. All treatment plans were normalized to deliver maximum dose of 12 Gy-Eq to mucosa in oral cavity and pharynx, and whether each tumor location can be eligible for BNCT with adequate dose distribution were evaluated. The tissue area that can achieve over 20 Gy-Eq for the minimum dose to the tumor was regarded as the efficient treatment field eligible for BNCT.

Results: The volume of efficient treatment field had large variability depending on tumor location. For all cases, the depth of shallowest and deepest site of the efficient treatment field from skin were 0.6 ± 0.4 (0 – 1.3) cm and 4.7± 1.2 (2.2 – 6.5) cm. Therefore, the efficient length of depth direction of the efficient treatment filed was 4.0 ± 1.5 (1.3 – 6.5) cm. As for orbital (6.5cm), parotid gland (5.9cm), maxillary (5.3cm) and nasal cavity (5.1cm) tumors, the depth of deepest sites were more than 5 cm from the surface of the skin. And they were less than 3 cm for oral cavity (2.3 cm), cervical II lymph node (2.8 cm), buccal mucosa (2.9 cm), and glottis (1.2 cm). Depending on these results, the parotid gland tumor was able to be given extremely higher dose. The tumors localized in oral cavity had a relatively lower dose than tumors at the upper site of oral cavity, such as the parotid gland, orbita, maxilla. The ethmoid sinus, nasopharyngeal, and mesopharyngeal tumors were considered to have poor eligibility for BNCT because of the deeper location.

Conclusion: Tumor location might become an important clue to judge treatment indication in head and neck BNCT.

Keyword: head and neck cancer, dose distribution, efficient treatment field

Parallel Session

Pa P4 01

Improvement of gamma-ray telescope system for BNCT at Kyoto University Reactor

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Introduction
A gamma-ray telescope system for BNCT has been settled at Heavy Water Neutron Irradiation Facility (HWNIF) in Kyoto University Reactor (KUR). This system has been utilized mainly for the on-line and real-time estimation of the boron-10 concentration averaged in whole of liver, in BNCT for multiple hepatic tumor. This system is under improvement in order to be effective in BNCT for the other body-part tumors, such as brain tumors, head and neck tumors, lung tumors, breast cancers, etc.. As a part of this improvement, the collimator was improved for expanding the effective telescope field.

Materials and Methods
One of the defects of the old gamma-ray telescope system was the limitation for the adjustment of the effective telescope-field. This was caused from that the field was adjusted only by one collimator which was settled just before the detector. Then, it was decided that the mechanism for the field adjustment was changed. The collimator part was divided to two parts, such as the upper part for patient side and the lower part for the detector side, and the interval between the upper and lower collimators was changeable. Rotary drive mechanism was adopted for the movement of the upper and lower collimators, because the larger space was not necessary for this mechanism. The design study for this new collimator system was performed by the simulation calculation using a Monte Carlo simulation code, MCNP, for the diameter of the collimators and the interval between the collimators.

Results
It was resulted from the simulation calculation, that the effective telescope-field could be adjusted almost from 2 to 20 cm, by changing the collimator interval from 0 to 150 cm, in the case of the 2-cm collimator diameter.

Conclusion
The new collimator system based on the simulation results, was completed in March 2018. This system will be settled at KUR-HWNIF on June 2018. We have a plan to perform the experiment for the characteristic estimation at KUR-HWNIF, in order to confirm the efficacy of the improved gamma-ray telescope system. This study was supported by The Kyoto University Research Fund (Core Stage Back-up, in 2017).

Keyword: gamma-ray telescope system, prompt gamma-ray, boron-10 concentration, Kyoto University Reactor

Pa P4 02

Dosimetric influence of respiratory motion in boron neutron capture therapy for plumonary tumor

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IIntroduction: The feasibility of Boron Neutron Capture Therapy (BNCT) for lung tumor has been mentioned in previous studies. However, influence of patient respiration was not considered for not only irradiation but also treatment planning. The aim of this study to investigate the influence of tumor motion that induced by patient respiration to the dose distribution of the clinical target volume (CTV) and organ at risk (OAR) in BNCT.

Methods and Materials: Five patients who were underwent stereotactic body radiation therapy for pulmornary tumor (upper, middle, and lower region of lung) in their real life. Because this study is to evaluate the influence of respiratory motion on dose of CTV and OARs, two patients with small respiratory movemnt (less than 10 mm), and three patients with large movement (more than 10 mm) were selected. 4D-CT images were acquired under free breathing, sampled at 0.5s intervals for the reference phase (mid ventilation). CT images were imported into the Tsukuba-plan, versions 2016 beta. The target regions were delineated as tumor at each image. 6 mm additional margin was applied to the tumor for generation of CTV. Lung and liver were also delineated as OAR, respectively. Although ideal irradiation method for to treat pulmornary tumor has been mentioned in previous study, single field was used to only evaluate influence of respiratory motion on the dose of CTV and OARs in this study. Beam line was set on the centroid of CTV at reference phase and approched surface of the patient. Treatment plans were generated for iBNCT;

the accelerator power was 16 kW, the irradiation time was one hour, the irradiation aperture was 120 mm. The doses were calculated using monte-calro calculation algorithm with a grid size of 2.5 * 2.5 * 1 mm. Dose volume histgram analysis of CTV and OARs werer performed. The minimum dose of CTV as CTV D98, the mean dose of CTV as CTV D50, V9.1 Gy of liver, and V7.0 Gy of lung were compared between reference plan and other plans. Forthermore, we investigated feasibility of respiratory gating technique in BNCT.

Results: In the evaluations of dosimetric influence of respiratory motion, when the tumor is located upper, middle region of lung, there were no significant differences. However, CTV D98 and D50 decreased approximately 5% at lower region. Nevertheless, there were no significant differences OARs under each constrains. Using respiratory gating technique that except end inhalation, CTV D98 and D50 did not differ significantly. By contrast, treatment time was 1.3 times compared with non-gating irradiation.

Conclusions: In this research, we investigated the influence of resipiratory motion on0 the dose distribution in BNCT for plumonary tumor. The results have shown that the influence of respiratory motion was small at upper, and middle region of lung. However, when the tumor is located at the lower region, there were significant differences between reference plans and other plans. Especially, when the tumor is located near the liver, its influece was huge. In addition, we also simulated respiratory gating technique, which can achieve feasible treatment time with suppression of its influence.

Keyword: BNCT, Plumonary tumor, Respiratory motion,

Pa P4 03

e_LiBANS project: thermal and epithermal neutron sources based on a medical Linac

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The E_LIBANS project (INFN, CSN 5) aims at producing neutron facilities for diverse interdisciplinary irradiation purposes among which pre-clinical research for BNCT. After the success setting up and characterize of the thermal neutron source based on a medical LINAC a similar apparatus for epithermal neutrons is under development. Both structures are based on an Elekta Precise SL 18 MV, installed in a dedicated bunker at the Physics Department of Turin University. In both cases the linac head is coupled with a photo-converter-moderator system which deploys the (γ, n) photonuclear reaction on a thick lead target to convert the bremsstrahlung photons of the linac beam into a neutron field. Suitable materials and geometries are chosen to slow down neutrons to the wanted energy and to reduce the gamma contamination and the residual fast-neutrons component in the irradiation cavity. A pure thermal spectrum, with flux intensity rounding 106 - 107 cm-2 s-1 has been achieved with the present configuration and an epithermal one is foreseen with the new photoconverter. Materials as Teflon and aluminum are used to slow down neutrons without completely thermalize them. A further borated shield is employed to reduce the thermal component.
Together with the sources development, studies on active neutron diagnostics able to work in high rate conditions are carried on by the Elibans collaboration. Some of these detectors have been used to qualify, in a metrological way, the neutron field generated with the thermal source.
This communication describes the results of the last experimental measurement carried on with the thermal source and illustrates the project of the epithermal facility showing the MCNP6 simulation previsions and the expected achievements. Furthermore, results from the diagnostics development are presented both for the thermal and epithermal neutrons detection.
Acknowledgments
The LINAC facility at Department of Physics in Turin has been funded by the University of Turin and the Istituto Nazionale Fisica Nucleare, with contributions from Compagnia di San Paolo and Fondazione CRT.

Keyword: Neutron sources, Photonuclear, Neutron detectors

Pa P4 04

The influences of moderator geometry on beam quality of Li-target based AB-BNCT

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Introduction: The beam-shaping assembly (BSA), especially moderator, directly affect the neutron beam quality. In order to obtain the optimum neutron beam, the relationship between the moderator geometry and the beam quality was valuated in this paper.

Materials and methods: In this study, simulation was conducted by phits. The energy of incident proton was 2.5 MeV. Boundary condition was set that the distances from the targets to the export surfaces of moderators were the same. Finally, 18 different cases for both Cylinder and truncated cone moderators were simulated with volumes varies from 25, 000 to 75, 000 cm3. To evaluate the neutron beam quality, IAEA recommendation for BNCT beam was referred; a modified Snyder head phantom was used to evaluate dosimetric performance; and γ dose profile of the entire export surface of BSA was calculated. The 10B concentration for normal tissue and tumor was 18 ppm and 63 ppm separately. The dosimetric performance including advantage depth (AD), 30 RBE-Gy treatable depth (TD), and irradiation time was calculated according to the dose limit of 11 and 12.5 Gy for skin and brain, respectively.

Results: The irradiation time increased with increasing moderator volume, furthermore, the dosimetric performance was independent of the moderator geometry. If the cylinder and the truncated cone moderator has same volume, the differences of TD and irradiation time were within 3 %. Nevertheless, different moderator geometry had significant influences on the export surface γ dose. During the treatment of the whole irradiation time, the γ dose per surface area of truncated cone moderator BSA was 9.76 % less than that of cylinder.

Conclusion: Under certain moderator volume condition, the dosimetric performances of the cylinder and the truncated cone moderators made little difference. Considering the γ dose of the export surface, the truncated cone moderator could be a better choice.

Keyword: beam-shaping assembly, moderator geometry, boron neutron capture therapy

Pa P4 05

A Simplification in BNCT Treatment Planning: Two-component Treatment of Inhomogeneous, Multi-component Dose Distributions, Based on Dose-Fraction Regularity

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IIntroduction
BNCT treatment planning is at a developing stage because of large uncertainties in biological indices in the planning, such as TCP and NTCP. The uncertainties stem from those in the determination of radiobiological parameters, but they are compounded by complex dose distributions involved in BNCT. The dose distributions are complex because of their being multicomponent and highly inhomogeneous. Methods handling the complexity are getting to be established, but because of numerous voxels in DICOM data, their application is still complicated in clinical situations, especially when iso- effective dose method is applied.
We propose a reduction of this complexity by applying dose-fraction regularity, observed in our BNCT dose simulation, that fractional (i.e. %) doses of components are nearly independent throughout tumor voxels. Utilizing the regularity, each of multi-component (i.e. mixed) dose distributions is then formulated as a one- or two-component dose distribution: Because the effective α and β (in LQ model) of a voxel for mixed radiation depend solely on the dose fractions of the mixed radiation, the survival fraction (SF) of a voxel is expressed as SF of one component, or a product of two SF's; one for the boron doses and the other effectively representing all non-boron doses. DVH is obtained directly from the dose dependence of SF with its parameters. If needed, CBE and (effective neutron) RBE are determined from the DVH as subsidiary indeces for the chosen definitions.

Materials and Methods
Simulations are carried out by the use of a modified Snyder head phantom, in which a voxel model of a malignant glioma, depicting a clinical BNCT treatment. The model consists of 56 cubic voxels of 1 cm3 in the 4×4×4 configuration with the four corners missing, and the central top is 2 cm below the scalp surface. The adult compositions of brain, skull, and scalp are taken from ICRU Report 46. The 10B concentrations (in BPA) used are 60 and 15 μg/g in tumor and normal tissues, respectively. Neutron beams of a circular shape (10 cm diameter) go through the central axis of the voxel configuration. The neutron beam fluence is set so that the maximum weighted-dose in normal tissues is a tolerable amount, chosen to be 12 Gyw (evaluated with the RBE/CBE values commonly used in Japan). The simulation is carried out by the use of PHITS ver. 2.88 with the neutron beams of eleven mono-energies from 1eV to 30 keV and also of the energy spectra of the KURRI accelerator and reactor, and the Tsukuba accelerator, by taking from the literature.

Results
The observed regularity: The dose fractions by all mono-energetic beams and KURR accelerator beams are found to remain approximately the same through all energies and in all voxels. For example, in the case of one-component formulation, the dose fractions of the Boron, proton, and gamma are 76.2(1.3), 6.0(1.1), and 17.8(2.2) % with (one STD), respectively, for the neutron spectrum of KURR accelerator. Using the (multi-component) α and β values of Coderre et al (1993), the one-component values are computed to be 0.937(0.013) and 0.0008(0.0004) for all voxels, respectively. A RBE/CBE value evaluated at the cold spot (9.30 Gy, SF=1.94E-4) instead of 10% SF is close to that of the iso-effective dose in the large volume %. The two-component formulation and numerical results for all neutron spectra will be also shown in the presentation.

Conclusion
Inhomogeneous, multi-component BNCT dose distributions are reduced effectively to one- or two-component distribution, using the dose-fraction regularity. In this simplification, the uncertainlties in DVH used in clinical situations are directly related to those in survival fractions deterined bio-radiologically.

Keyword: BNCT treatment planning, Dose-fraction regularity, Survival fraction, DVH

Pa P4 06

Evaluation of Multi-field Technique Applied to Boron Neutron Capture Therapy for Brain Tumors

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In Taiwan, clinical trials of boron neutron capture therapy (BNCT) for the recurrent Head-and-Neck (H&N) cancer started in August 2010 using the epithermal neutron beam of Tsing Hua Open Pool Reactor (THOR) under the collaboration of National Tsing Hua University (NTHU) with Taipei Veterans General Hospital (TVGH). In recent years, the advancement in accelerator-based neutron source for BNCT makes this radiotherapy modality more appealing to the medical doctors. In March 2017, treatment of brain tumors using BNCT at THOR started with more medical doctors involved.
Among the various dose constraints prescribed by the doctor for the brain tumors treatment, the maximum dose and the average dose of normal brain are the commonly limiting factors on the irradiation. Therefore, in contrast to previous H&N cancer BNCT treatment at THOR, two-field technique was commonly adopted in our BNCT treatment of brain tumors to enable the increase of the average/minimum tumor dose under the same dose constraints. This study evaluates the advantage of multi-field technique for brain tumors of different sizes and depths.
BNCT treatment planning was performed by using our in-house treatment planning system, THORplan, in which 18F-BPA PET image was used to obtain tumor-to-normal tissue ratio of boron concentration. Dose criteria for normal brain were set to be < 10 Gy-w, and < 2 Gy-w in average. By operating THOR between 1.2 to 1.8 MW, the irradiation can usually be completed in 40 mins, in which ~ 15 mins for each field and 10 mins for patient repositioning.
It was found that, if the dose limit is due to the constraint on the maximum brain dose, using two-field technique can reduce the maximum dose of normal brain and thereby the average tumor dose and minimum tumor dose can be increased under the same dose constraints. If the dose limit is due to the constraint on the average brain dose, the two-field technique has little effects on the average tumor dose, but is helpful in increasing the minimum tumor dose. Using three-field irradiation can further increase the minimum tumor dose, but usually results in decrease of the average tumor dose. Three-field irradiation has not been adopted in our patient treatment so far.

Keyword: Boron Neutron Capture Therapy (BNCT), brain tumors, treatment planning, multi-field technique

Pa P4 07

Status of BNCT Neutron Generator Development at the IAP RAS

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BNCT development nowadays is constrained by a progress in neutron sources design. Creation of a cheap and compact intense neutron source would significantly simplify trial treatments avoiding use of expensive and complicated nuclear reactors and accelerators. D-D or D-T neutron generator is one of alternative types of such sources.
A few years ago it was suggested to use a so-called high current quasi-gasdynamic ECR ion source with plasma heating by millimeter wave gyrotron radiation in a scheme of D-D neutron generator. Ion source of that type was developed at the Institute of Applied Physics of Russian Academy of Sciences (IAP RAS), Nizhny Novgorod, Russia. In a pulsed mode, it was demonstrated that it can produce deuteron ion beams with current density up to 700-800 mA/cm2. Using a 70 keV, 200 mA deuteron beam and TiD2 target neutron yield of 10^10 s^-1 was obtained.
The next step in the research is a transition to continuous wave (CW) operation. To continue development of the CW gasdynamic ion source a new experimental facility is under construction at the IAP RAS. Future source will utilize 28 and 37, 5 GHz gyrotron radiation for plasma heating. Overview of the obtained results and the status of the new source development will be presented. According to estimations, ion source output parameters would be enough for development on its basis of a CW D-D neutron generator with neutron yield about 10^10 – 10^11 s^-1. It is assumed that such neutron source could be perspective as a comparably compact device for boron neutron capture therapy studies.
Presented work is being supported in frame of realization of Federal targeted program R&D in Priority Fields of the S&T Complex of Russia (2014-2020) contract #14.604.21.0195 (unique identification number RFMEFI60417X0195).

Keyword: neutron generator, high current ion source

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Pa Ph5 01

Computational evaluation of dose distribution including radiation exposure to ambient organs for BNCT treatment combined with X-ray therapy or proton beam therapy

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Introduction
A team headed by University of Tsukuba is now in progress boron neutron capture therapy (BNCT) project in cooperation with KEK and some facilities. In the project, we also developed new Monte Carlo based treatment planning system (TPS) named Tsukuba-Plan. The beam delivery system and beam source information of the BNCT facility were already installed in TPS and is now moving to the verification stage of the TPS.
In recent radiotherapy, treatment combining multiple modalities is sometimes performed, so there is a possibility that X-rays or proton beams are combined with BNCT. Therefore, we have been improved the TPS so that dose distribution of not only BNCT but other radiotherapy can be calculated. Particularly, in case of treatment with a combination of multiple radiotherapy beams, the dose given to normal tissues is also important as well as the dose distribution of target. Monte Carlo based TPS can evaluate radiation exposure of ambient normal tissue including neutrons generated secondarily.
In this study, we evaluated the dose distribution and radiation exposure including ambient organs for BNCT treatment with X-ray therapy or proton beam therapy combination by using Tsukuba-Plan.

Materials and Methods
We selected Particle and Heavy Ion Transport code System (PHITS) as Monte Carlo code.
First, the beam delivery system for therapeutic X-ray therapy beams were correctly constructed using the PHITS code. Additionally, the beam delivery system for proton beam therapy by the double scattering irradiation was also constructed as precisely as possible. The ridge filterers, equipment for creating uniform dose distribution around the tumor, were designed based on the design drawing and reproduced the clinically well-used Spread-out Bragg peak (SOBP) width of 20 mm to 100 mm. The calculated three-dimensional absorbed dose distributions (i.e. percentage depth dose: PDD and off-center ratio: OCR) of X-rays or proton beams in water phantom were compared with experimental data. In addition, the three-dimensional dose distributions by neutrons generated with irradiation of the incident beams were calculated by PHITS code.
Finally, CT images of the whole body human-shaped phantom were read into Tsukuba-Plan, and a virtual BNCT treatment plan was created. We tried to summarize various dose distributions assuming a treatment that combine the X-ray therapy or proton beam therapy to the treatment plan of BNCT. The dose given to ambient normal tissue was evaluated separately for influence by incident beam spread and secondary generated neutrons.

Results
The calculated PDDs and OCRs for therapeutic X-ray beams in the water phantom were

good agreement compared with the experimental data. We also succeeded in reproducing the coordinates of MLC accurately in PHITS. Therefore, it was possible to evaluate the dose distribution with respect to the complicated irradiation fields of X-ray therapy.
The calculated PDDs and OCRs for therapeutic proton beams with various widths of SOBP in the water phantom were completely good agreement compared with the experimental data. By accurately reproducing the beam delivery system of the therapeutic proton beams, it became possible to evaluate the three-dimensional distribution and energy spectrum for secondary generated neutrons as well by Tsukuba-Plan. We accomplished the evaluation of dose distribution with the human-shaped phantom in the case of BNCT combined with X-ray therapy or proton beam therapy. Furthermore, not only the main beam component but also the secondary generated neutrons can be evaluated in the evaluation.

Conclusion
Tsukuba-Plan can calculate and superimpose absorbed dose distributions of X-ray therapy or proton beam therapy on the dose distribution of BNCT. It is possible to evaluate not only the target dose but also the dose given to the surrounding normal tissues including incidental neutrons by using Tsukuba-Plan.

Keyword: MonteCarlo calculation, Dose evaluation, TPS

Pa Ph5 02

Accelerator Based Neutron Capture Therapies in France

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Introduction In France, we are working on an interdisciplinary project 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) coming from neutron physics and detection expertise, the Institut of Advanced Biophysics (IAB) coming from radiobiology, biological research, the CERMAV from biological chemistry and the Grenoble University Hospital (CHU) from clinical experience.

Material, Methods and Results
At the LPSC, we are working on:

- A rotating Be target 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 a new dedicated facility.
- The design of a Beam Shaping Assembly (BSA) adapted to this rotating target will be described giving an optimized ed rate of capture at the tumor level.
- The development of a fast neutron directional detector (MIMAC-FastN) to characterize and control the neutron fields produced at the target level.

Conclusion
We will present the status of the Be target, its moderator and the fast neutron directional detector (MIMAC-FastN) able to characterize the fluence and the angular distribution of the neutron fields produced. We will describe the calibration using a thin foil of natB inside the active volume, with the same nuclear reaction that will be produced at the tumor level. We will show measurements of fast neutrons performed recently.

Keyword: Targets, BSA moderators, Neutron detection

Pa Ph5 03

BNCT FACILITY AT MARIA REACTOR – FINAL KICK-OFF: BEAM TEST, OPENING RESEARCH STATION, CONSTRUCTION OF BUILDING FOR REACTOR LABORATORY FOR BIOMEDICAL RESEARCH AND PROGRESS IN FORMULATION PROGRAMME OF "NEOBOR" SCIENTIFIC PLATFORM

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Introduction
As a result of 10 years preparation BNCT facility at MARIA reactor is successfully opened. In the paper it will be presented effects of Work Packages defined for years 2016/2017. Four most important of them concern irradiation technology (tech), dosimetry (dosi), chemistry (chem) and biology (biol). Two first WP were done in NCBJ.

Materials and Methods
(Tech) Neutron beam is produced in the core of MARIA reactor and conduced by medial channel positioned in the reactor pool and after geometric and energetic forming in the horizontal channel (concrete shielding of reactor) is focused on paramedical research stand. It will be presented each part of the system i.e. intelligent converter for beam in-

tensity modulation, adjustable filter-moderator system for energy spectrum change, beam shutter, beam stopper and equipped irradiation room with dosimetric and radioprotection system. All supporting research laboratories will be placed in special building and progress of it construction will be presented.
(Dosi) Shape and intensity of the beam separately for gamma and neutrons i.e. four commonly used for BNCT dose components measured with recombination methods (unique technique) compared to other methods (active and passive). It is expected to full-run of neutron beam with intensity of 2x109 n/cm2/s in the 2019. The set of four recombination detectors: (1) hydrogen free to measure external gamma radiation and from the capture reaction 1H(n, γ)2D, (2) tissue-equivalent to distinguish gamma and total neutron dose, (3) nitrogen for detect protons from 14N(n, p) reaction and extracting thermal neutrons and finally (4) boron fluoride for boron dose determination from the 10B(n, α)7Li reaction fulfil needs of four dose determination for medical protocols in BNCT.

Results and conclusion
Basing on MARIA facility the scientific network "Neobor" was formed. Several Polish, European and Asian research institutions have already signed the Letter of Intent for collaboration in BNCT research. In the paper it will be presented scientific programme. After notification of the uniqueness of this treatment method and beginning of creation a BNCT training, educational and research BNCT station in the reactor, the cooperation between people from Polish scientific society sixteen institutions such as research centres or oncology centres declared their intent to be a team member. Through the group meetings organized on the basis of scientific workshops and their involvement in biological, chemical, medical and material research interdisciplinary laboratory was launched. 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, National Research Centre - Kurchatov Institute, University of Tsukuba and finally Lukaszczyk Oncology Centre and Polish Military and University Medical Institute as medical partners. As a result preliminary studies of usage borated nucleosides as a boron carriers for BNCT will be presented (Chem) and first experiments of boron cluster conjugates with macromolecular carriers and small molecules will be presented (Biol). Additionaly preliminary results of experiments of impair the biological activity of the T regulatory lymphocytes by boron cluster antibody conjugates, thereby enhancing the cytotoxic T cells and use of phagocytic cells as carriers of insoluble boron derivatives (boron carbide, boron nitride) to their deliver and deposit in tumour tissues will be presented in the paper. "Neobor" intended also to investigate BNCT for the treatment of certain autoimmune disorders.We have

Keyword: BNCT, neutron beam, dosimetry, radiobiology

Pa Ph5 04

Comparison of Shielding Calculation Methods for an AB-BNCT Facility Based on the Be(p,xn) Reaction with 30 MeV Protons

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Introduction
The Tsing Hua Open-Pool Reactor (THOR) was upgraded and renovated for boron neutron capture therapy (BNCT) application in 2004. Clinical trials for patients with locally recurrent head and neck cancer were started since August 1, 2010. THOR has been used for over 50 years and now is operating under its second license extension. The BNCT group in Taiwan is seeking to establish an accelerator-based BNCT (AB-BNCT) facility to continue and expand its research activities. The proposed facility is based on the neutron production via the Be(p, n) reaction with 1 mA 30 MeV protons. A specially designed beam shaping assembly (BSA) will be installed to deliver a high-quality epithermal neutron beam for BNCT purpose. The basic layout of the proposed facility includes an accelerator room and a patient treatment room; the BSA is embedded in the partition wall between the two rooms to reduce radiation leakage and simplify the shielding design. This study investigated the characteristics of the radiation field around the facility and compared the performance of various calculation methods in shielding analysis.

Materials and Methods
Five calculation methods were employed in this study to estimate the dose rate distribution around the facility. Using the Monte Carlo transport code MCNP6, method 1 was a straightforward simulation including proton bombardment and radiation transport of secondaries around the facility. Compared with method 1, method 2 used a common variance reduction technique of geometrical splitting and Russian roulette to improve the MCNP6 computational efficiency. Method 3 additionally employed a coupling technique called the surface source write and read (SSW/SSR) implemented on the exterior surfaces of the BSA, allowing for the reuse of the generated radiation source in subsequent shielding calculations. Method 4 was an ADVANTG/MCNP5 run, which automatically implements the Forward-Weighted Consistent Adjoint Driven Importance Sampling (FW-CADIS) methodology for generating space- and energy-dependent weight windows and a consis-

tent biased source distribution. Method 5 estimated dose rates outside the bulk shielding based on a point-source line-of-sight approximation, where the source terms and attenuation lengths were pre-generated by a series of Monte Carlo simulations in simplified configurations.

Results

Methods 1-4 were all continuous-energy Monte Carlo simulations but with different variance reduction techniques. They showed consistent predictions on the dose rate distribution of the facility. However, their computational efficiencies varied substantially. The computational efficiency of method 1 without user-requested variance reduction was unacceptable in this case because the simulation run for about 20 days on a desktop computer and barely provided meaningful results outside the shielding walls. Method 2 substantially improved the computational efficiency and provided statistically converged dose rate predictions. Although the computational efficiency of method 3 was similar to that of method 2, it was a useful technique for shielding optimization because it can eliminate the computing burden of source generation in repeated calculations corresponding to various shielding configurations. Taking advantage of approximate 3D forward and adjoint transport solutions, the performance of method 4 surpassed those of methods 2 and 3 by more than a factor of 10 for tallies of most interest in this case. Compared to accurate but time-consuming Monte Carlo simulations, method 5 is a quick and practical approach for preliminary shielding design, which has been shown can yield fairly accurate or conservative estimates for the transmitted doses.

Conclusion

Monte Carlo simulations are generally considered the most accurate method for solving complex shielding problems. However, it is time-consuming in nature and effective variance reduction techniques are indispensable for problems involving deep penetration. Approximate but simplified methods are often preferable in design phase, especially when the facility layout is expected to undergo several changes. Taking the proposed AB-BNCT facility as an example, this study considered five calculation methods for estimating the dose rate distribution around the facility and compared their performances in terms of accuracy and computational efficiency. The results and experience obtained from this study will be useful for those performing similar analyses and our future design work toward the first AB-BNCT facility in Taiwan.

Keyword: Accelerator-based boron neutron capture therapy, Shielding calculation, FW-CADIS

Pa Ph5 05

Opportunities for therapeutic beam monitoring with single-moderator spectrometers

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Introduction

A step forward in the field of neutron spectrometry was given, in recent years, by the introduction of single-moderator spectrometers. These devices succeeded in the difficult challenge of condensing the functionality of a Bonner Spheres Spectrometer into a single moderator, embedding multiple thermal neutron detectors. To meet the measurement needs of different types of neutron producing installations, two geometries were developed: the spherical one for isotropic measurements (SP2 device), and the cylindrical one for directional measurements (CYSP device). As the internal thermal neutron sensors are simultaneously acquired, these devices are suited to operate as real-time beam monitors with spectrometric capabilities. This communication will explain the operating principles, characterization and performances of these instruments, with special emphasis on a new design that will lead to an operational active device (CYSP-NCT) intended for rapid and precise spectrometric measurements in neutron capture therapy facilities.

Materials and Methods

The new design of a single-moderator spectrometer for NCT applications (CYSP-NCT) consists of a series of active thermal neutron detectors (TNDs) located along the axis of a polyethylene cylinder. The size of the cylinder (lower than 45 cm height x 35 cm diameter) were optimized to eliminate the contribution from neutrons coming from other directions with respect to that identified by the collimator, considering a maximum neutron energy of 0.5 MeV (therapeutic range). The internal locations of the TNDs were selected to achieve similar spectrometric capabilities as a Bonner Sphere spectrometer with diameters from 8 cm up to 25 cm. CYSP-NCT consists of two main blocks, namely the collimating aperture (front part) and the detecting capsule (rear part). The detecting capsule contains the TNDs, plus a lateral protection made of borated rubber and high-density

Parallel Session

polyethylene. The TNDs are silicon-based detectors (≈ mm2 sensitive area) covered by an optimized 6LiF radiator. CYSP-NCT response matrix was derived with MCNPX.

Results
The simulated response matrix of CYSP-NCT shows that the device will have spectrometric capability similar to that of a Bonner Sphere spectrometer with diameters from 8 cm up to 25 cm. Experimental tests on the TNDs showed that, even in very intense neutron fields with important photon contribution, the detector reading is not affected by the photons. TND linearity as a function of the neutron fluence rate was also tested, with satisfactorily results.

Conclusions
Owing to the expected characteristics in terms of spectrometric capability, good linearity and photon rejection, simple and real-time operation, and reasonable size, the CYSP-NCT is very promising for the routine characterization of the neutron beam in NCT facilities.

Keyword: Single moderator neutron spectrometer, CYSP, CYSP-NCT, unfolding, neutron beam monitor

Pa R2 01

5-aminolevulinic acid can sensitize malignant glioma to boronophenylalanine-based boron neutron capture therapy

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Introduction
Malignant gliomas (MGs) are the most frequent primary brain neoplasms in adult and still incurable brain tumors with current therapeutic options. As in other cancers, highly tumorigenic subpopulations with stem cell-like features have been identified within malignant gliomas, known generally as “cancer stem cell”. Glioma stem cell (GSC) is considered to be responsible for treatment resistance and ultimately for tumor recurrence. Recent evidence indicates that GSCs can be divided into two mutually exclusive subtypes with phenotypic and genetic differences, “Mesenchymal” (MES-GSC) and “Proneural”: The former shows more aggressive phenotype and is more resistant to chemoradiotherapies than the latter.
BNCT is a tumor-selective particle radiotherapy, which have been clinically applied to treat malignant neoplasms including gliomas. We are also conducting a multicenter Phase I/II clinical trials of boronophenylalanine (BPA)-based BNCT to treat the patients with MGs in hospital. BPA is a 10B-derivative of phenylalanine, transported into tumor cells through neutral amino acid transporters. However, further improvements in BNCT seem to require the development of new boron-drugs or any way to sensitize GSCs to BNCT.
5-aminolevulinic acid (ALA) is a natural amino acid and the first metabolite in the heme biosynthesis. Exogenous ALA selectively accumulates into malignant neoplasms and is converted to fluorescent porphyrins, mainly protoporphyrin-IX (PpIX), in the tumor cells. Thus, ALA has been widely used as a prodrug of photoactivatable PpIX to detect tumor tissues in glioma surgery, which actually contributes to the safe and maximum resection of MGs. In our previous study, we found that ALA significantly increase the intracellular concentration of neutral amino acids including phenylalanine in GSCs. The aim of this study, therefore, is to examine whether ALA can sensitize MG to BPA-based BNCT using a mouse brain tumor model implanted with MES-GSC; more intractable GSC phenotype.

Materials and Methods
In this study, we used a human MES-GCS cell line (GB13) and a mouse GSC cell line (TS). GB13 is established from a clinical specimen of MG, classified into mesenchymal subtype by genome-wide transcriptome analysis. TS is an artificial GSC made by overexpressing H-RASV12 in normal neural stem cells isolated from the subventricular zone of adult B6 mice harboring a homozygous deletion of the INK4a/Arf locus.
Using ICP, we measured intracellular boron concentration of GB13 and TS, 6 hours after incubation of 10 ppm BPA-containing medium, following 24 hours pre-incubation with 0, 0.03, 0.1, 0.3 or 0.9 mM of ALA. For in vivo BNCT, GB13-intracerebraly implanted animals were randomly divided into 6 groups; control, ALA-only, neutron-irradiation only, ALA- neutron-irradiation, BNCT only, ALA-BNCT. 80 mg/kg of ALA was orally given to animals 24 hours prior to BPA administration. Gene expression of LAT1 and ATB, neutral amino acid transporters, in the formed brain tumors were examined using qPCR.

Results
Pre-incubation with ALA significantly increased the intracellular accumulation of BPA in

Parallel Session

GSCs in ALA-dose dependent manner. In vivo biodistribution assay for BPA, the preloading of ALA improved the intratumoral boron concentration and the tumor/normal brain boron ratio in the MES-GSC-implanted brain tumor model. Accordingly, the animals in ALA-BNCT group showed significantly longer survival than those in BNCT only group. Gene expression of ATB significantly increased by ALA in vivo.

Conclusion
Our data suggested that ALA can act as a drug delivery enhancer for BPA through up-regulating of ATB in glioma, and can improve the therapeutic efficacy of BPA-based BNCT. Since both BPA and ALA have an ability to accumulate into glioma cells, ALA is expected to efficiently exert tumor-selective sensitizing effect, when used in combination with BPA-based BNCT.

Keyword: Cancer stem cell, 5-aminolevulinic acid, BPA, amino acid transporters

Pa R2 02

Evaluation of folate receptor targeted novel boron compound for boron neutron capture therapy using rat brain tumor model

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Introduction
Folic acid (FA) has high affinity for the folate receptor (FR), which is limited-expressed in normal human tissues and over-expressed in many cancer cells. It was also reported that FR is over-expressed in malignant glioma, especially in glioblastoma. FA is expected as an optimal target ligand for selective delivery to cells, because of its ease of conjugation to therapeutic agents and its high affinity for the FR, even after conjugation to its therapeutic agents. we developed a novel pteroyl closo-dodecaborate conjugate (PBC) in which the pteroyl group is known to interact with FR. We evaluated the cytotoxicity of PBC in vitro BNCT, and the therapeutic efficiency compared to boronophenylalanine (BPA) using F98 glioma-bearing rats in vivo BNCT.

Materials and Methods
We evaluated the boron concentration of F98 glioma cells for three 10B compounds, BPA, borocaptate sodium (BSH) and PBC in vitro, and the biodistribution of these following BPA administrated intravenously (i.v.) or PBC administrated by convection-enhanced delivery (CED) in F98 glioma bearing rats. For in vitro BNCT study, the cytotoxicity of each boron compound was evaluated with a colony forming assay. And, for in vivo, F98 glioma bearing rats were divided to five groups: untreated controls, neutron irradiation controls, BNCT with BPA (i.v.), BNCT with PBC (CED), and BNCT with combination of BPA (i.v.) and PBC (CED).

Results
In vitro, PBC attained higher cellular uptake F98 glioma cells compared with BSH, but less than BPA. In vivo biodistribution study, however, the PBC (CED) 6h after termination group attained highest boron concentrations of tumor (64.6 ± 29.6 μg/g). The corresponding ipsilateral normal brain concentrations were low (2.7 ± 1.8 μg/g). Median survival times (MST) of untreated and irradiated controls were 23 (21-24) and 26 (22-29) days, respectively, while rats that received PBC(CED), followed by BNCT, had a MST of 31 (26-36) days, which were similar to those obtained following i.v. administration of BPA (30 (25-37) days). And the combination group had a MST of 38 (28-40) days. PBC(CED) group showed higher tumor boron concentrations than BPA(i.v.), but it was approximately equal without significant difference in survival time. In combination of PBC (CED) and BPA (i.v.), a significant prolongation in survival time was obtained compared with the single agent groups.

Conclusion
It seems that tumor boron concentration appears high due to extracellular accumulation of PBC administered by CED, but this is not considered to be true tumor cellular uptake. And we did not compete for the curative effect by using PBC together with BPA and accepted meaningful duration of survival time. This study suggested the possibility that PBC became the drug to add curative effect for BNCT.

Keyword: folate receptor. folic acid, F98 glioma bearing rat, boron compound

Pa R2 03

Radiobiology experiments for thermal and epithermal RBE factors in BNCT

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Introduction

Some aspects of the current radiobiology of BNCT have been questioned since years. The relative biological effectiveness (RBE) factors corresponding to each dose component is a crucial aspect. The RBEs have been systematically taken as constants despite the fact that they depend on the dose, neutron energy, tissue and endpoint. A value of 1 for photon dose is always assumed as well as a constant CBE depending on the compound. However, the aim of this project is to establish RBE factors for the thermal and epithermal component.

The difficulty of measuring the effect of the recoil protons from the nitrogen capture has resulted in the assumption of a total proton dose with the same RBE factor for thermal and epithermal neutrons. Previous studies have described values ranging from 1.4 to more than 10. Furthermore, it is not recommended to apply RBE factors, estimated in a specific facility, to a different one. Given that the main difference between facilities is the maximum energy, the low energy neutron RBEs should be similar in all of them. Hence it is of crucial importance that this factor is well estimated for different tissues and in isolation from the epithermal factor.

Materials and Methods

A series of experiments are proposed to being carried out at Institut Laue-Langevin. At this facility, there is a cold neutron beam line with thermal equivalent capture flux of 2·10^9 ncm-2s-1 and 2'5·10^-8 MeV average energy. With low gamma component and almost not epithermal dose thanks to the bent guide, it results in a very "clean" beam. An excellent place to measure the effect of low energy neutrons. To isolate the effect of nitrogen capture, 15-nitrogen cell labeling is also on the experiment plan.

In addition, another series of experiments with same cell lines will take place at an epithermal beam in CNA Seville. To compare the effect with photons, a hospital blood irradiator will be used.

Results

Tumour cells lines from melanoma, glioblastoma and head and neck carcinoma were irradiated in the different neutron and photon sources. As well as healthy cell lines like embryotic kidney, lung fibroblast and mesenchymal stem. Results will be shown and comment.

Conclusion

New data for biological estimation of neutron effect in BNCT is necessary. These in vitro experiments with different cell lines is the beginning of a data library for RBE for different neutron energies, tissues and endpoints.

Keyword: radiobiology in BNCT, Relative biological effectiveness, nitrogen capture, Institut Laue-Langevin

Pa Ch3 01

A novel boron-derived tyrosine serves as a theranostic agent for positron emission tomography and boron neutron capture therapy

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INTRODUCTION

Non-invasive diagnosis of cancer has been a long-standing challenge in cancer management. A biopsy or surgery is often required to justify the malignancy of certain types of cancer and to obtain T/N ratio. Imaging-guided BNCT could provide accurate location of tumor region to avoid unnecessary irradiation of normal tissues. Moreover, imaging with derivatives of boron delivery agents could provide tumor-normal tissue (T/N) ratio to facilitate patient screening and treatment planing. Previously, 18F-FBPA-PET, the standard non-invasive technique for imaging-guided BNCT, proved to be a success. However, FBPA is not BPA after all. The pharmacokinetics of two molecules are not completely identical, which affects the precision and accuracy for the pre-diagnosis for BNCT to a certain extent. Herein we report a boron-derived amino acid with high tumor specificity and tumor accumulation which also can be radiolabeled as a probe for PET imaging without altering the molecular structure.

MATERIALS AND METHODS

A boron-derived amino acid (BAA) was synthesized to mimic natural amino acid, of which the transportation depends on L-type amino acid transporter (LAT). 18F-19F isotope exchange reaction was conducted for radiolabeling and quality control was performed by both HPLC and radioTLC. The metabolic stability of 18F-BAA was assessed both in vitro and in vivo. PET imaging and boron concentration evaluation were performed in mice bearing B16-F10, GH3 and A549 xenografts on the shoulder.

RESULTS

The intracellular uptake of BAA was highly selective and competed effectively with natural amino acid. Moreover, BAA is highly metabolically stable, which is a unique advantage comparing with other boron agents because rapid metabolism often results in low tumor-specificity with high background uptake. As expected, 18F-BAA showed high accumulation in B16-F10 tumor (8.60 ± 1.5 %ID/g) and GH3 tumor (7.53 ± 1.8 %ID/g) and low uptake in the rest of the body. The tracer had predominant renal clearance but with low kidney retention. Remarkably, 18F-BAA co-injected with therapeutic dose of non-radiolabeled BAA (1000 mg/kg) still showed high-specific accumulation in the tumor along with low uptake in other major organs according to PET imaging results. The tumorous boron concentration of B16-F10 mice reached 20.2 ± 4.0 ppm with high tumor-muscle ratio (2.7 ± 0.5) and high tumor-brain ratio (10.2 ± 1.2).

CONCLUSION

A boron-derived amino acid (BAA) was developed and evaluated for PET imaging of cancer and boron delivery for BNCT. BAA exhibited high tumor accumulation and high T/N ratio. 18F-BAA-PET provided clear visualization of tumor xenografts in mice. Furthermore, the signal of 18F-BAA would not be blocked by therapeutic dose of non-radiolabeled BAA, indicating that PET imaging with 18F-BAA could represent the actual BAA distribution. In summary, BAA holds great potential to be a efficient boron delivery agent for imaging-guided BNCT.

Keyword: Boramino acid; Theranostic; PET; BNCT

Pa Ch3 02

Rational Designed Boronated Porphyrin Loaded Micelle Meet the Shortcoming of Small Molecule Boron Agents for Boron Neutron Capture Therapy

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INTRODUCTION

Boronated porphyrins are particularly promising among all the newly developed boron delivery agents due to their demonstrated high accumulation and long retention in cancer cells, low toxicity, possibility to combine photodynamic therapy (PDT) with BNCT and most essentially, the potential imaging properties such as fluorescence imaging and PET imaging to locate tumor region and carry out quantification of tissue-localized boron which facilitate treatment planning. The early reported boronated porphyrins BOPP and CuTCPH shown excellent performance during preclinical biological investigations which were placed in great expectation. However, clinical applications of boronated porphyrins are held back by low tumor-blood ratio and direct toxic effect on platelets found in phase I clinical research. PLGA-PEG-based nanocomplex has been widely used for drug delivery due to its biocompatibility, biodegradability and tumor specificity. Herein, we report a novel Boronated Porphyrin loaded PLGA-PEG Nanocomplex (BPN) as an efficient agent of multimodal molecular imaging and boron delivery for BNCT.

MATERIALS AND METHODS

Porphyrin structure within BPN served as the fluorophore for in vitro and in vivo optical imaging and the chelator of 64Cu for PET-imaging. The metabolic stability and toxicity of BPN was assessed both in vitro and in vivo. PET imaging and bio-distribution studies were performed in mice bearing B16-F10 and 4T1 xenografts on the shoulder. Fluorescence imaging were performed in mice bearing 4T1 xenografts on the back. Neutron irradiation treatment were performed on mice bearing B16-F10 xenografts with a thermal neutron beam of 1012 neutron per cm2 in IHNI.

RESULTS

The intracellular uptake of boron in cultured B16-F10 cells incubated with BPN solution(50 μM boron) for 48 h was up to 150 ppm. Boron concentration within tumor meets

the therapeutic requirement at 24 h after administration. Remarkably, both PET imaging and fluorescence imaging showed fast clearance and long tumor retention (24 h post administration). The tumor-to-muscle and tumor-to-brain ratio was up to 5.7 ± 0.9 and 11.7 ± 1.8, respectively. As expected, the median survival time mice treated with BPN (75 mg boron/kg) and neutron irradiation was significantly elongated than those treated only with neutron irradiation.

CONCLUSION
A novel boronated porphyrin loaded PLGA-PEG nanocomplex was developed and evaluated for diagnosis and treatment for BNCT. BPN was able to perform efficient delivery of boron both in vitro and in vivo. Administration of BPN (or 64Cu-BPN) allowed for clear visualization of tumor xenografts in mice, suggesting a unique advantage of multimodal molecular imaging targeteing tumor for the guidance of BNCT. In summary, BPN is holding great potential of being an efficient theranostic agent for cancer management.

Keyword: Micelle; Boronated Porphyrin; PET; BNCT

Pa Ch3 03

An innovative therapeutic approach for malignant mesothelioma treatment based on the use of Gd/Boron multimodal probes for MRI guided BNCT

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Introduction.
Malignant Mesothelioma (MM) is an aggressive tumour with a poor prognosis whose incidence and mortality is a function of past exposure to asbestos, after a latency period of 30-50 years. MM is recognized as a rare occupational disease lacking of any significant therapies and the median survival after diagnosis is less than 9-12 months. MM is a disseminated tumour, spreading inside the whole pleura or peritoneum. In such scenario, conventional radiotherapy has limited effectiveness due to the presence of several radiosensitive tissues which limit the maximum dose deliverable to the malignant nodules. Therefore, to improve both the clinical diagnostics and treatment, the discovery of new MM potential target molecules is of great interest. The aim of this study is to develop an innovative imaging guided approach based on Boron Neutron Capture Therapy, for the treatment of mesothelioma, assisted by the quantification of the in vivo boron distribution by MRI. To this purpose a dual BNCT/MRI agent (AT101) has been synthesized and delivered to tumour cells using Low Density Lipoproteins as specific carriers. The innovation of this study lies on the test of novel theranostic agents, able to maximize the selective uptake of boron atoms in tumor cells and, at the same time, to quantify the in vivo boron distribution in the tumor and in other tissues by MRI. The measurement of local boron concentration is crucial to determine the optimal neutron irradiation time, to calculate the delivered radiation dose and to evaluate the toxicity of the treatment by determining differences in boron concentration between tumor and healthy tissues.

Materials and Methods.
Flow cytometry (FACS) analysis was carried out to evaluate LDLRs expression on the membrane of ZL34 and AE17, human and murine mesothelioma cell lines, respectively. Cells were incubated 30' with a monoclonal antibody (mAb) specific for LDLRs and then with the FITC-labeled secondary Ab. Boron and Gd cells uptake was assessed by ICP-MS and MRI on ZL34, AE17 and two healthy (MRC−5 and NMuMg) cell lines. An in vivo model was prepared by subcutaneous injection of ZL34 cells in Nu/Nu mice. Gd and boron concentrations have been obtained by the signal intensity enhancement of T1 weighted images acquired before and after theranostic agent administration. BNCT has been performed at the TRIGA-Mark II reactor at the University of Pavia.

Results.
The herein reported results demonstrate, for the first time, that overexpressed LDL receptors can be successfully exploited to deliver to mesothelioma cells a therapeutic dose of boron (=26 µg/g), significantly higher than in the surrounding healthy tissue (=3.5µg/g). Since, human ZL34 mesothelioma internalized a significantly higher amount of boron with respect to both healthy and murine cells, the human model has been selected for in vivo studies. Moreover, the presence of a Gd complex in the BNCT agent allows the boron quantification before starting neutron irradiation. After irradiation with thermal neutrons, tumor growth was evaluated for 40 days by MRI. Tumor masses of boron treated mice showed a drastic reduction of about 80-85%.

Conclusion.
One may conclude that BNCT seems to be a treatment particularly efficient on this rare

pathology especially when the therapeutic boron is delivered to the tumor cells at high concentrations with high selectivity exploiting LDL transporters. This study is a typical example in which a highly selective therapy takes advantages from imaging to improve its efficacy. These encouraging results could take on an even more important significance as, thanks to the new neutron sources based on proton accelerators, new BNCT centers are being set up directly in hospitals

Keyword: Mesothelioma, Low Density Lipoproteins, MRI, carboranes, Gd contrast agents

Friday, November 2, 2018

Pa Ph6 01

Recent Development of BSA in D-BNCT

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D-BNCT(Dongguan Boron Neutron Capture Therapy) is a new experimental facility and will complete the construction at the end of this year in CSNS campus. Using 3.5MeV proton energy directly from RFQ and 10MeV upgraded by DTL in the near future, two types of neutron generated target including the solid lithium and beryllium target will be options. The recent development of the structure and thermal-hydraulic design of solid lithium target, and the optimization design of the BSA design coupling with the target will be shown here.
The design of target is a multi-phycis problem, especially the compact structure design, low melting point of lithium under high heat flux, and the deposition of lithium layer. The Optimization of structure design is calculated with Ansys, and thermal hydraulic design is completed with FVM method. For the high thickness and size of lithium layer in target, the uniformity is difficult to control. The evaporation process of lithium is simulated with FEM method, and the results are compared with experiment data, which from the evaporation equipment specially designed for large size. Coupled with the target, the optimization of BSA with 3.5MeV proton energy and different moderator materials are carried out with Monte Carol simulation code, also the air activation in the treating room is calculated.

The structure of target also consider the replacement of solid lithium target to beryllium target. From calculation results, the target can both meet the demand of solid lithium and beryllium. Under high heat flux, the maximum of cooper based in target below 140 degC which can be used as based for solid lithium. From the calculation and experiment results of the profile of lithium layer based on the evaporation equipment, the uniformity is reasonable and the equipment can be used to deposit lithium layer to the target. Results from the Monte Carol simulation give the suitable moderator material and its thickness, and the air activation in the treating room is under limited.
The calculation and experiment results show that the design of the target and BSA can meet the engineering requirements.

Keyword: D-BNCT, Deisgn, lithium Target, BSA

Pa Ph6 02

D-BNCT Project in China

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D-BNCT (Dongguan BNCT) project was launched at Dongguan Neutron Science Center, the campus of China Spallation Neutron Source(CSNS), on the basis of the technology in the construction of CSNS and ADS(Accelerator Driven Subcritical System) projects.
This is an accelerator-based BNCT facility. BNCT neutrons are generated from a Lithium target bombarded by a proton beam from an intense beam RFQ linac. The RFQ accelerator was built for an ADS project and thus designed for CW operation. It routinely operated at 3.5MeV beam energy and 4.5mA beam average current in pulsed mode about 10 years ago. Further increasing its beam duty factor is planned for the D-BNCT project and it is expected to reach a beam power more than 35kW on a solid lithium target for epithermal neutron flux of 1E9 n/cm^2/s. The Lithium target R&D and he detailed design study of BSA are underway. In addition to the neutron generator, Boron drug of BPA is also under development at HEC Pharm (Hopeful Energetic Corporation). D-BNCT is a joint project, and now the major parts are CSNS and HEC Pharm. The local government and HEC Pharm financially support this project. Construction of the D-BNCT facility is in good progress and we expect to start animal test at D-BNCT in the early next year at relatively low beam power. And then gradually increase power for target high-power test.

Promoting hospital operation in wide spread in China is our final target and thus this D-BNCT project is only our starting point in our BNCT course. After the success of this project, we are going to build a new BNCT facility in a hospital for preclinical test.
This paper will present the overall design and current construction status of the project, as well as our plan for future development of BNCT.

Keyword: D-BNCT project, RFQ linac, Lithium target

Pa Ph6 03

Study of neutron production and moderation for Sulfur Neutron Capture Therapy

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Neutron capture therapy with Sulfur-33, like boron neutron capture therapy with Boron-10, has a feasibility of curing some kinds of tumors, ocular melanoma in particular. The key point of sulfur neutron capture therapy is whether neutron beam fluence and the resonance capture cross section of 33S(n, α)30Si reaction at 13.5 keV can reach the radiotherapy requirement. In this paper, authors studied 13.5 keV neutrons production and moderation based on accelerator neutron source. A lithium glass detector was used to measure the neutron fluxes produced via near threshold 7Li(p, n)7Be reaction with the time of flight method. Furthermore, the moderation effects of different kinds of materials were studied by the means of Monte Carlo simulations.

Keyword: Sulfur Neutron Capture Therapy, Boron Neutron Capture Therapy, 7Li(p, n)7Be neutron source

Pa Ph6 04

Compact Accelerator-Driven BNCT System Used Sealed Lithium Target

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(Introduction) Low energy protons incident on lithium target are one of the most suitable reaction for the accelerator-based BNCT, because a sufficient flux and good quality of epi thermal neutron beam can be obtained by using a compact beam shaping assembly (BSA) and low activation of accelerator facility can be reduced the radiation exposer for medical staffs. However, metalic lithium has several difficulties in chemical properties (low melting point, high chemical activity and 7Be production) as a target material. For resolving those isssues, we are developing a compact and sealed Li target in combination with a DC accelerator. We are constructing a compact accelerator-driven neutron source to confirm the practical reliability and performance of the sealed lithium target for the BNCT application in the Nagoya University.

(Material & Method)
Metalic lithium on the target base plate is cvered by a titanium foil. Low-energy and high current proton beam (2.8MeV, 15mA) is passing through the titanium foil and irradiates the lithium. 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/m2. Neutrons with the energies of less than 1MeV are produced due to the 7Li(p, n)7Be reaction under the irradation of the 2.8MeV proton beams. The fast neutrons are moderated by a compact beam shaping assembly (1m in dia.) with a nozzle to meet all the specidications indicated in the IAEA-TECDOC-1223. The sealed lithium target, which will be strongly activated, will be changed routinely by using a remote handling sytem.

(Results)
For the neutron production experiment, we had completed to construct an additional neutron shield around the sealed lithium target and the BSA in the accelerator room and are preparing neutron diagnostic system. We will report a first experimental result in the conference.

Keyword: Lithium target, DC accelerator, Compact BSA

Pa Ph6 05

Current Status of Research and Development Boron Neutron Capture Therapy in Indonesia

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Abstract. Boron Neutron Capture Therapy (BNCT) is an advanced form of radiotherapy technique that is potentially superior to all conventional techniques for cancer treatment, as it is targeted at killing individual cancerous cells with minimal damage to surrounding healthy cells. After decades of development, BNCT has reached clinical-trial stages in several countries, mainly for treating challenging cancers such as malignant brain tumors. The Indonesian consortium of BNCT already developed the design of BNCT for treatment of many cases of cancer types using many neutron sources. In this occasion, the testing report of collimator and shielding design for Kartini Research Reactor (KRR) are presented. The main manufactured-collimator material used is 99%-pure nickel, while the paraffin material is used for the main shielding material with an aluminum casing. The functional tests were done by measuring particles (neutron and gamma) flux and dose at the aperture and outside of the paraffin shielding, respectively. At 100 kW power of the reactor, the total neutron flux measured were 3.2890×105 n/cm2s, with thermal neutron flux were 2.5602×105 n/cm2s, and fast neutron flux were 7.2883×104 n/cm2s. Average of neutron and gamma dose outside the paraffin shielding were 215μSv/h and 0.58 μSv/h, respectively. In addition, the preliminary study of dose calculation for in vivo/in vivo test using KRR neutron source also conducted for cancer cell which were placed inside the whole-body phantom. The boron concentration was varied from 10mg/g, 20mg/g, 30mg/g, 40mg/g and 50mg/g, with the cancer depth varied from 1 to 5 cm. The study was a simulation-based experiment using Monte Carlo method which was applied in the Particle and Heavy Ion Transport Code System (PHITS).

Keyword: BNCT, Kartini Research Reactor, in vivo/in vitro, MCNPX

Pa R3 01

BIODISTRIBUTION STUDIES OF MALEIMIDE-FUNCTIONALIZED CLOSO-DODECABORATE ALBUMIN CONJUGATES (MID:BSA) IN THE HAMSTER CHEEK POUCH ORAL CANCER MODEL

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Introduction Squamous cell carcinoma of the head and neck region is the sixth most common cause of cancer deaths worldwide. The relatively poor overall 5-year survival rate for malignancies of the oral cavity and the fact that radical surgery causes large tissue defects poses the need for more effective and less toxic therapies. The requirements for successful BNCT are preferential accumulation and retention of a non-toxic 10B carrier in a tumor, a sufficiently high absolute concentration of 10B in tumor tissue (at least 20 ppm) and targeting of all tumor cell populations. The development of new, more tumor-selective, non-toxic and effective boron delivery agents is probably the single greatest need for the future progress of BNCT. Recently, nano carrier-based boron delivery systems have been developed to improve the efficacy of BNCT. Previous studies focused on a serum albumin as a nano biocarrier that accumulates in malignant and inflamed tissues due to enhanced permeability and retention (EPR) effect. Furthermore, since tumor is the major site of serum albumin catabolism, serum albumin has been extensively investigated as a versatile carrier for therapeutic and diagnostic agents. Nakamura et al. previously developed maleimide-functionalized closo-dodecaborate (MID) for conjugation to bovine serum albumin (BSA). MID was found to conjugate not only to the free SH of the cysteine residues but also to lysine residues in BSA under physiological conditions. The highly boronated BSA (30 mg B/kg) showed high and selective accumulation in tumor 12h post-administration and a significant BNCT effect in colon tumor-bearing mice. Herein we performed biodistribution studies of MID:BSA in the hamster cheek pouch classical oral cancer model, previously proposed and validated by our group for BNCT studies in head and neck cancer. Materials and Methods 6 hamsters cancerized with the classical cancerization protocol (DMBA application twice a week during 12 weeks) were

selected. One hamster was injected intravenously (IV) with MID:BSA 30 mg B/kg (21.1 mg MID: 307 mg BSA). Two additional hamsters were injected IV with MID:BSA 15 mg B/kg (10.5 mg MID:154 mg BSA). Samples of blood (n=2), tumor (n=6), precancerous (n=2) and normal (n=2) pouch tissue, spleen (n=2), liver (n=2) and kidney (n=2) were taken 12h post-administration and processed for boron concentration measurements by ICP-OES. A group of 3 hamsters were used for biodistribution studies at 19h post-administration. Results The 30 mg B/kg MID:BSA hamster exhibited high BSA toxicity (internal bleeding and cardiorespiratory arrest). The IV injection of 15 mg B/kg MID:BSA at a slow rate (0.05-0.1 ml/minute) prevented BSA toxicity and was well tolerated. The boron concentration in tumor was 38.3 +/- 11.4 ppm, 14.1 ppm in precancerous tissue, 6.6 ppm in normal pouch tissue, 16.6 ppm in spleen, 31.1 ppm in liver, 27.6 ppm in kidney and 47.3 ppm in blood. Tumor/Normal tissue, Tumor/Precancerous tissue and Tumor/Blood boron concentration ratios were 5.7+/-1.2, 2.8+/-0.2 and 0.8+/-0.2, respectively. At 19h, tumor still showed a potential therapeutic value (27+/-7.9 ppm) while blood had cleared (26.1+/-2.3 ppm). Tumor/Normal tissue relation was still higher than 4. Conclusion BSA toxicity is a consideration when injecting a compound conjugated to BSA and depends on the animal model studied. Therapeutically useful tumor boron concentration values and tumor/normal tissue ratios were demonstrated for MID:BSA in the hamster cheek pouch oral cancer model. Thus, MID:BSA would be a promising new boron compound that warrants further assessment. If ongoing additional biodistribution studies confirm the present trend, in vivo BNCT studies will be warranted to assess the actual therapeutic effect of MID:BSA-BNCT in the hamster cheek pouch oral cancer model. The role of high boron concentration values in blood remain to be determined in radiobiological BNCT studies.

Keywords: MID:BSA, new boron compounds, biodistribution studies, oral cancer, hamster cheek pouch

Pa R3 02

EVALUATION OF THE RADIOPROTECTIVE EFFECT OF OLIGO-FUCOIDAN TO REDUCE DERMATITIS AND MUCOSITIS INDUCED BY BNCT IN ORAL CANCER AND ECTOPIC COLON CANCER MODELS

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Introduction The hamster cheek pouch oral cancer model and the ectopic model of colon cancer in BDIX rats are used in our group for BNCT studies. They also allow us to study the radiotoxic effects of BNCT: mucositis and dermatitis, respectively. Both adverse responses affect patient's quality of life during and after treatment. If severe, they would limit the dose of radiation or, even worse, would lead to the interruption of the treatment schedule, which could negatively impact treatment efficacy. Consequently, managing radiation-induced mucosa and skin injuries during and after treatment is an important aspect of cancer care, with high economic costs. Despite technological advances in radiation delivery and growing interest in managing mucosa and skin reactions, there is no gold standard in the management of radiation mucositis and dermatitis. Previous studies in our group demonstrated the value of histamine to reduce severe mucositis in the oral precancer model. However, there is still room for improvement in this field. Oligo-Fucoidan has recently drawn considerable attention because it has several beneficial functions, including anti-inflammatory and anticancer activities. The aim of the present study is to evaluate the radioprotective effect of Oligo-Fucoidan in our oral cancer hamster cheek pouch model and in the ectopic model of colon cancer in BDIX rats, in terms of reducing severe mucositis and dermatitis respectively. Materials and methods An initial study involved a group of 6 BDIX rats bearing tumors in the right hind flank. BDIX rats were injected subcutaneously in the right hind flank with 1 × 106 DHD/K12/TRb syngeneic colon cancer cells in 100 µl of F10-DMEM culture medium (GIBCO). Three weeks later, the tumor-bearing legs were treated locally with BPA-BNCT at RA-3 Nuclear Reactor and Oligo-Fucoidan (200mg/ml) administered orally, once a day, starting the day prior to irradiation and continuing for 14 days after BNCT (total 16 days). Oligo-Fucoidan was kindly provided by Hi-Q Marine Biotech International Ltd (Taiwan). The powder was dissolved in double-distilled H2O and stirred at 25°C for 30 min. Previous studies in this model performed in our group showed that BPA-BNCT induced severe dermatitis (erythema, dry and moist desquamation) in this model. Results and Conclusions Ongoing studies are currently under evaluation and will be reported. Future studies in the oral cancer hamster cheek pouch model will be performed to study the effect of Oligo-Fucoidan to avoid or reduce BNCT-induced severe mucositis. Acknowledgments We gratefully acknowledge the provision of Oligo-Fucoidan by Hi-Q Marine Biotech International Ltd (Taiwan), and the efforts of Ming-Chen Hsiao to promote these studies.
A MONTI HUGHES and VA TRIVILLIN contributed equally.

Keyword: BNCT, Oligo-Fucoidan, Radioprotector, Dermatitis, Mucositis

Pa R3 03

BORON NEUTRON CAPTURE THERAPY (BNCT) COMBINED WITH BCG AS IMMUNOTHERAPY IN AN ECTOPIC COLON CONCER MODEL: LOCAL AND ABSCOPAL EFFECTS

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Introduction: Colorectal cancer (CRC) is the most common gastrointestinal cancer in the United States and is the third most common malignant diagnosis in both sexes. The mechanism of action of Bacillus Calmette-Guerin (BCG) is unclear but it is known to display an immediate response of unexpected nonspecific type followed by a specific response against tumor cells. The abscopal effect refers to the inhibitory action of radiotherapy on tumor growth at a site distant from the area of irradiation, mediated by radiation-induced immune responses. We demonstrated the abscopal effect of BNCT that combines selective tumor uptake of 10B compounds and neutron irradiation. However, irradiation coupled with immunotherapy could amplify the local effect on the tumor and also the immune response induced by radiation to elicit a robust Abscopal effect. The aim of the present study was to evaluate the local therapeutic efficacy of BNCT combined with BCG as immunotherapy in the BDIX rat ectopic colon cancer model and assess the abscopal effect.

Materials and methods: BDIX rats were inoculated subcutaneously (sc) with 1x106 DHD/K12/TRb syngeneic colon cancer cells in the right hind flank. Four weeks post-inoculation, tumor-bearing rats were injected with borono-phenyl-alanine (BPA) intravenously (iv) and the tumor nodule was locally irradiated at RA-3 at a maximum absorbed dose to the healthy leg volume (considered as skin) of 7.8 Gy (BNCT-group, n=27). A second group of tumor-bearing rats were treated similarly but injected with three intratumoral applications of BCG (0.2 mg/0.1 ml per injection, viability 6x105 CFU) 1, 7, and 14 days post BNCT (BNCT+BCG-group, n=9). A third group of tumor bearing rats were treated with BCG only (BCG-group, n=10). The Beam only-group (BO-group, n=3) was exposed to the same neutron fluence as the BNCT-group, with no prior boron compound injection. The (BO+BCG)-group, n= 3 combines the two previous groups. The Sham-group n=29 consisted of untreated tumor bearing animals exposed to the same manipulation. Two weeks post-BNCT, 1x106 DHD/K12/TRb cells were injected sc in the contralateral left hind flank in all BDIX rats. Inhibition of tumor growth in the contralateral flank to yield tumor volumes below 50 mm3 was considered indicative of Abscopal effect (mean tumor volume in the contralateral flank of Sham animals was 198 +/- 186 mm3). Once weekly for 7 weeks post BNCT the tumor volume (TV) was measured in both legs. Animal experiments were approved by IACUC.

Results: A significant local therapeutic efficacy was observed in the BNCT-group and BNCT+BCG-group vs. Sham-group $p = 0.0006$ and $p = 0.000001$ respectively. A statistically significant percentage of animals exhibiting Abscopal effect was observed in the BNCT-group (22%, 6 of 21), BCG-group (40%, 4 of 10) and BNCT+BCG-group (56%, 5 of 9) while in the Sham group only 3% (1 of 29) of the animals exhibited a contralateral tumor volume below 50 mm3 (49 mm3).

Conclusion: The present study would demonstrate a marked and enhanced therapeutic efficacy when BNCT is combined with an immunological therapy such as BCG, associated to a more robust Abscopal effect.

Keyword: BNCT, BCG, Abscopal Effect, Immunotherapy, DHD/K12/TRb cells

Pa R3 05

DYNAMIC INFRARED IMAGING FOR BIOLOGICAL AND PRECLINICAL STUDIES IN BNCT

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INTRODUCTION
Dynamic Infrared Imaging (DIRI) is a noninvasive technique, complementary to clinical follow-up in diverse areas of medical and biological research. It is based on the detection of the infrared radiance emitted by the area under evaluation, acquired and processed by

high sensitivity infrared thermal cameras, providing real-time temperature distributions during transient processes. The technique was implemented in our group for follow-up of BNCT melanoma patients and was also incorporated in different preclinical studies.

MATERIALS AND METHODS

We present the results of the observations in the following contexts:

I) Study of the evaporation process in histological sections for neutron autoradiography.

II) Assessment of the characteristics of tumors, precancerous and normal tissues and radiation-related mucositis in the hamster cheek pouch oral cancer model.

III) Assessment of the skin toxicity associated with the irradiation of rat legs in a protocol to study the abscopal effect of BNCT.

IV) Study of the effects of tissue temperature rising during the application of electrical currents, in an electroporation protocol in the hamster cheek pouch oral cancer model.

V) To understand the temperature evolution during explanted organ cooling in a preclinical protocol designed to investigate normal tissue radiation tolerance for ex-situ BNCT irradiation in sheep lungs. A FLIR model T420 infrared camera with temperature sensitivity around 50 mK was used. Ambient temperature and relative humidity are measured to characterize, through heat transport models, characteristic quantities like transient time constants. For the cheek pouch and rat leg models, air currents at ambient temperature were employed in some instances to observe the response of the tissue under a mild thermal stress. In the other experimental settings, the processes are inherently time-dependent.

RESULTS AND CONCLUSIONS

I) A good correlation was found between temperature plateaus (associated with change of state) during tissue water evaporation of histological sections and their weight loss, providing additional information regarding the spatial distribution of water migration, revealed by a non-homogeneous temperature distribution.

II) Evaporative cooling caused by the eventual presence of surface moisture in the pouch mucosa that develops post-irradiation toxicity may mask underlying inflammatory or metabolic processes important in clinical evaluation. To uncouple this effect, wrap films were used to measure the real tissue temperature. With the film, animals with severe mucositis exhibited a higher mean temperature than animals with moderate mucositis. Their asymptotic temperatures without film (at the end of the observation) remained above room temperature, contrary to what was observed in animals with moderate mucositis.

III) During the weeks where acute inflammatory responses may develop, temperature measurements in the irradiated leg compared with the non-irradiated contralateral leg showed significant differences and completely different evolutions during the application of air currents, consistent with an inflammatory condition where the irradiated leg lacks a full vasoconstrictor response under thermal cooling stimuli, contrary to what is observed in the contralateral leg and the rat tail.

IV) During the application of high voltage electrical currents to the tumors, applied to favor the influx of drugs, the tissue temperature undergoes high and fast temperature excursions. These measurements can be coupled to electrochemical models to verify the assumptions and provide information about possible alterations of the tissue under study.

V) In order to preserve explanted organ viability, the temperature of the lung must be lowered up to 6°C. For this, the lung is completely perfused with preservation solution at 4°C during 20 to 30 minutes while it remains on a tray filled with crushed ice. We determined the temperature evolution in different parts of the explanted lung and characterized the time constants that are helpful for optimizing the procedure.

Keyword: Dynamic Infrared Imaging, Infrared Thermography, Preclinical Studies

Pa B3 01

Intra cellular boron distribution evaluation by neutron autoradiography

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Introduction

The selectivity of Neutron Capture Therapy is due to the biological targeting of chemical compounds containing atoms such as B or Gd. To date, only two boron compounds have been clinically used: sodium borocaptate and boronophenylalanine. The different

localization of boron inside cells obtained with different formulations may change the effectiveness of BNCT. Efforts are being dedicated to develop new borated formulations which increase boron uptake in cancerous cells. The evaluation of new compounds is not trivial, there are many experimental methods capable of measuring the average boron concentration in tissues or liquid samples. Few of these techniques can evaluate the macroscopical boron distribution, while the sub cellular boron distribution is limited to complex methodologies. In this work, we show how we managed to overlap an optical image of cells with the optical image of boron distribution, by using a semi-standard neutron autoradiography technique.

Materials and Methods

The autoradiography technique is based on a CR-39 detector which is a passive Solid State Nuclear Track Detector (SSNTD). We combined it with a microscope containing a robotic stage, which we used to reposition the CR-39 and capture the overlapping optical images. To perform this, we marked the CR-39 in 3 points, which we used as reference to evaluate the position of the picture. Experiments were performed on HeLa and ZL34 human mesothelioma cells, exposed to different borated formulations. Once the SSNTD is marked cells were made grow directly on the detector, exposed to the borated formulation, then fixed to take optical images. Subsequently, the CR-39 was irradiated in a thermal neutron field in the thermal column of the research nuclear reactor TRIGA Mark II of Pavia University. After the irradiation, the SSNTD was etched in NaOH, and tracks were visualized by using the aforementioned optical microscope.

Results

By irradiating the cell mono-layer grown on the CR-39, for 2 hours at full reactor power (250 kW) and by developing the image for 20 minutes at 70o in 6.25M of NaOH, the superficial density of tracks was suitable for the image reconstruction. The marks made on the detector were used to define the position of the cell images and to compute the repositioning of the CR-39 after the irradiation, with a precision of approximately 1 μm.

Conclusion

The final overlaid image shows that this autoradiography set-up can be used to evaluate the sub-cellular boron distribution, giving a valuable information on the capacity of a borated vector to carry 10B atoms inside critical cellular structures. Further studies are ongoing in order to standardize the technique and make it a robust tool for the evaluation of novel BNCT carriers.

Keyword: Boron, imaging, subcellular

Pa B3 02

Use of EpiskinTM to evaluate BNCT radiation damage to healthy tissue

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Introduction

Models to evaluate the clinical outcome of Boron Neutron Capture Therapy (BNCT) are based on in-vitro and in-vivo experiments. Parameters that are evaluated in such experiments are boron uptake and Compound Biological Effectiveness (CBE) for a specific borated compound in a cell line. These data are used to perform dosimetry evaluation for clinical BNCT. Anyhow, the multiple BNCT radiation fields that may be necessary for complex cases, complicates the endpoint evaluation, especially in healthy tissues. The prescription dose in a BNCT treatment is on the maximum tolerable dose to the healthy organ at risk exposed to the neutron field. In a number of cases, skin is found to be the limiting organ. Anyhow, in vitro models for healthy tissues are difficult to be used because the radiation damages that can be used as an endpoint are not easily connected to the survival. With this work we want to propose an alternative model to evaluate the limiting dose to the skin by using EpiskinTM which is an artificially reconstructed human skin cell layer. This method may offer an alternative to the animal models, whose employ is often limited by a number of factors such as costs, authorizations or lack of facilities.

Materials and Methods

Experiments were conducted at the research nuclear reactor TRIGA Mark II of Pavia University, in collaboration with biologists and chemists. A first characterization required the study of boron uptake and distribution in the samples. EpiskinTM cells were treated with BPA at the concentration of 80 ppm for different contact times: 4, 18, 24 hours. Two configurations were tested: cells surrounded by borated medium or cells in contact with medium only from below. Boron uptake in these tissue samples was measured by neutron

autoradiography, that was applied both for quantification of boron concentration and for imaging of boron biodistribution. The goal was to optimize the treatment conditions of cells to obtain a suitable boron concentration at least in the central part of the sample, and to get a sufficient uniformity of boron distribution. To gain a deeper insight into this new kind of sample, we experimentally evaluate the loss of weight when the sample dries out. Moreover, the effect of the thin cell support, necessary to grow the cells, was studied by alpha transmission experiments. Experiments are ongoing to irradiate EpiskinTM after BPA treatment, to study radiobiological effects as a function of the irradiation dose.

Results

Measurements by neutron autoradiography showed that it is possible to obtain a uniform boron distribution in the central part of the samples by exposing cells to BPA enriched medium for 4 hours, with better results if the samples are surrounded by medium. Imaging show that there is a higher boron concentration at the edge of the samples, that will be not considered for the next steps, because irradiation damage will be evaluated in the central area.

Conclusions

EpiskinTM is being proven a suitable model for BNCT studies, although a careful characterization is needed to optimize the treatment and evaluated the irradiation damages. In fact, the tissue layers can be kept alive only for a limited number of days. This work represents a preliminary evaluation of the employ of these in-vitro models as an alternative to the irradiation of animals, in a moment where new radiobiological data are needed to allow more refined dosimetrical evaluations.

Keyword: Normal, Healthy, tissue, model

Pa B3 03

Prompt gamma tomography for BNCT-SPECT: a feasibility study using a small animal phantom.

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Introduction

One of the main problems to be solved in Boron Neutron Capture Therapy is the measurement of B-10 spatial distribution in the patient during the treatment. This measurement can be done using Single Photon Emission Computed Tomography (SPECT) detecting the 478 keV gamma ray emitted in the 94% of captures by residual Li-7 ions. More than simply B-10 spatial distribution, the counting rate of these gammas is meaningful of the dose rate due to the neutron capture reactions in the patient thus allowing an in vivo, real time dose monitoring. To pursue the development of a BNCT-SPECT system, at Pavia University and INFN Unit is presently on-going the 3CaTS project whose aim is to test the feasibility of a room temperature semiconductor detector made of the alloy CdZnTe (CZT) as the photon sensitive volume of the BNCT-SPECT.

Materials and Methods

In the present study we evaluated the capabilities of a 5x5x20 mm^3 CZT prototype to reconstruct the tomographic image of a tissue equivalent phantom loaded with point like gamma sources (such as Na-22, Cs-137 and Co-57), small activated detectors (Cu wires) and F-18 water solutions. The small dimensions of the phantom were chosen to represent mice and rats presently used by the Pavia BNCT group in safety and efficacy tests of BCNT as alternative treatment for lung cancers and osteosarcoma. F-18 water solutions were used to simulate the disturbance of the B-10 uptake by the healthy tissues in the animal body, while the point like sources and the extended wires were used to simulate different situations in terms of tumour volume, respectively a small and well localised tumour compared to a bigger and extended one. We chose to use gamma emitting sources due to the present lack of a suitable and optimized neutron beam at the Pavia reactor laboratory. The tomographic reconstruction was carried out exploiting a home-made algorithm based on the Filtered Back Projection (FBP) method.

Results

Preliminary reconstructed tomographies of the gamma rays emitted by the radionuclides loaded in the small animal phantom have been recorded, demonstrating the capabilities of the CZT detector as BNCT-SPECT photon sensor at least in an ideal case, i.e. without the neutron and gamma background surrounding the detector during the measurement in a clinical BNCT facility. Further studies are required to evaluate the CZT performances in an radiation environment closest to the real measuring conditions.

Conclusions

To pursue the task of real time therapeutic dose monitoring during BNCT a CZT prototype has been tested as photon detector for tomographic reconstruction of the prompt gamma ray emitted during the neutron irradiation. Due to the lack of a proper neutron beam at Pavia reactor laboratory, ideal situations have been created inserting gamma sources inside a small animal phantom and reconstructing the tomographic images by an home-made program.

Keyword: BNCT-SPECT, real time dose monitoring, CZT solid state detector

Abstracts Posters

Tuesday, October 30, 2018

Group I

PS1 CI 01

Reirradiation of Locally Recurrent Head and Neck Cancer with BNCT or Proton Therapy: a Systematic Review

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Introduction

Reirradiation of locally recurrent head and neck (HN) cancer is often challenging in clinical practice due to previous full dose radiation. Particle therapy such as BNCT and proton therapy may play important role in local treatment because of their unique dose distribution. We performed a systematic review to compare reirradiation with BNCT and proton therapy in HN cancer.

Materials and Methods

Clinical studies of locally recurrent HN cancer after high-dose photon therapy with salvage outcomes and toxicities were identified through online database searching. Primary outcomes of interest were overall survival and locoregional control.

Results

Four studies of BNCT (118 patients) and 4 studies of proton therapy (247 patients) were included (reference shown below). Two-year locoregional control rate was 60-77% in proton studies (3 studies) and 5-28% in BNCT cohorts (3 studies). Fraction numbers of BNCT is 1-2 and of proton therapy is 13-35. Two-year overall survival was 32.7-69% in proton studies (3 studies), and 22-47% in 4 BNCT cohorts. Grade 3 or greater mucositis developed in 3.3-32%, 9.7-53% of the patients undergoing proton therapy and BNCT respectively. One proton study reported carotid rupture in 2.9% of the patients while 2 studies of BNCT reported 5.9% and 4.8% of patients with carotid rupture. Incidence of treatment related death was 2.9%, 5.4%, 5% and 0 in 4 proton studies, respectively. Only one BNCT study reported treatment related death in 4.8% of the patients.

Conclusion

BNCT was delivered in a shorter interval with less fractionation than proton therapy. Severe mucositis occurred more frequently in BNCT group. The treatment related death seemed to be lower in BNCT. It is difficult to compare the two radiotherapy techniques in terms of survival because of large heterogeneity among cohorts and small number of studies. Further randomized trials are needed to objectively compare BNCT and proton therapy for locally recurrent HN cancer.

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Keyword: Recurrent head and neck cancer, reirradiation, BNCT, proton therapy

Abstracts Posters

PS1 CI 02

Recycling 10B-enriched Boronophenylalanine in Urine of Patients with Recurrent Brain Tumor

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Introduction

Boron neutron capture therapy (BNCT) is a therapeutic method using neutron and boron-containing drugs to treat recurrent head and neck cancer and recurrent brain tumor. Boronophenylalanine (BPA) is the most commonly used compound for BNCT. BPA molecules are needed to be internalized by cancer cell through specific receptors, in which 10B atoms are feasible to capture neutron and immediately fragment into 4He and 7Li ions to destroy cancer cell. During clinical BNCT therapy, almost one liter of BPA solution (25 mg/mL) was injected into patient by an intravenous drip for 2 hours to achieve expected dosage (400 mg/kg body weight). The concentration of 10B in cancer cell was ranged from 30 to 60 ppm representing only a small amounts of 10B-BPA be internalized into tumor. This work is prepared to observe excretion of 10B-BPA in urine and evaluate the possibility of recycling the drug from urine.

Materials and Methods

Urine samples were collected from patients who accepted BNCT treatment. The first sample was collected before neutron irradiation (called sample I) and second sample was collected after neutron treatment (about 2.5 hours after 10B-BPA injection, called sample II). Samples are separated into four fractions by a workflow established in our laboratory and all fractions will be analyzed by (1) UV/Vis, (2) LC/MS/MS and (3) ICP-MS.

Results

Preliminary results showed: (1) Amounts of 10B-BPA in sample I and II was ranged from 15.56 to 119.4 mg and 523.6 to 1826 mg, respectively; (2) The trend of 10B-BPA concentration was D>A>>B, C; (3) Relative percentage of 10B-BPA in fraction D was more than 50% compared to A, B, or C fractions in sample II of various patients; (4) Total recoveries of 10B-BPA in sample 2 of various patients were estimated from 2.09% to 7.30% of total injected amounts of 10B-BPA.

Conclusions

This study provided a workable method to recycle 10B-BPA used for BNCT from urine of patients with recurrent brain tumor. The results demonstrated that not only 10B-BPA entered into tumor rarely and metabolized through urine but also could be recycled from collected sample, might be a resolution of 10B-BPA source.

Keyword: BNCT, 10B-enriched BPA, urine, recycling

PS1 CI 03

Boron neutron capture therapy in 45 patients with recurrent head and neck cancers who have no other treatment options.

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Introduction: Head and neck cancer (HNC) is the sixth most common malignancy worldwide and its global incidence has significantly increased over the past decade. Surgery is the standard treatment for those with resectable disease, followed by radio- and chemotherapy for patients with high-risk pathological findings at the time of surgical resection. Despite this combined approach, the majority of patients will develop local and/or regional recurrences and 20%–30% of them will develop distant metastases. Although a few patients with locoregional recurrence can be salvaged by surgery alone or in combination with re-irradiation, most of those with recurrent or metastatic disease only will qualify

for palliative treatment. In order to increase the overall survival (OS) rate and to further reduce treatment related damage to normal tissues, new treatment modalities are required for recurrent, therapeutically refractory HNC. 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 Cancers (HNC) in 2001.

Material and Methods: From December, 2001 to May, 2014, we have treated a total of 45 patients with recurrent HNC by means of 62 applications of BNCT. Histopathologically, there were 34 patients with squamous cell carcinomas (SCC), 7 with salivary gland carcinomas and 4 with sarcomas. All of them had received standard therapy and subsequently developed recurrent disease for which there were no other treatment options. All of the patients received intravenously either a combination of two boron containing drugs, sodium borocaptate (BSH, 5g) and boronophenylalanine (BPA, 250mg/kg) or BPA (500mg/kg) alone. In this report we will summarize the clinical results and outcomes of 45 patients with HNC who had received BNCT at either the Kyoto University Research Reactor Institute (KURI) or the Japan Atomic Energy Agency (JAEA) nuclear reactor.

Results: All of the patients had advanced disease and 21 of 45 (47%) had regional lymph node metastases and 12 out of 45 (27%) had distant metastases at the time of treatment. (1) Boron concentration ratios of tumor/normal tissue (T/N ratio), as determined by 18FBPA-PET imaging were 1.8-7.0 for SCC, 2.2-4.0 for sarcomas and 2.0-3.7 for parotid tumors. (1) Regression rates were CR: 23 patients (51%), PR: 13 (29%), SD: 3 (7%), PD: 5 (11%), and not evaluated (NE):1 (2%) patient. The overall patient response rate was 87%. (2) The mean survival time was 30.6 months and the 5 year and 10-year OS rates were 32% and 21%, respectively. (3) Survival times following BNCT ranged from 1 to 142 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 BNCT represents a new and promising treatment modality for recurrent or far advanced HNC in patients for whom there are no other treatment options.

Keyword: BNCT, head and neck cancer, BPA, BSH

PS1 Cl 04

Evaluation of the impact on a change of patient's posture from preplan with diagnostic images to treatment position in boron neutron capture therapy

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Objectives

In boron neutron capture therapy (BNCT), patients should be set up closer to collimator as much as possible for keeping effective neutron flux. To perform BNCT treatment as optimized plan from diagnostic CT or MR image datasets, it is important to reproduce the patient setup guided with the entry and exit points on skin obtained from preplan using the diagnostic images. However in head and neck BNCT, there is a large discrepancy of patient positioning between diagnostic images in a supine position and actual treatment in a sitting position, and the skin entry and exit points is displaced along with the change of patient posture. Therefore, the skin marking for guide is not reliable in head and neck sitting-positioned BNCT. In this study, we aimed to clarify the trend of deviations for skin entry and exit points of beam central axis derived from the difference between the assumed setup position and the actual treatment position.

Material and Methods

Five patients were assumed to receive BNCT for parotid cancer in a sitting position. At first, using treatment planning system SERA, the lesions were delineated and the beam entry and exit points on patient skin were preliminarily decided on previous diagnostic CT images. To detect the deviation of each point on skin in all neck region, 24 points of interests (POIs) were set on a skin surface of the neck. After the first CT scan was performed in normal supine position, patients were immediately set up in a supine position with a 45-degree neck rotation toward the contralateral side, followed by the second CT scan. Furthermore, patients were set up in a pseudo-sitting treatment position by adding "bending forward" with a 30-degree waist pad, followed by the third CT scan. After matching three CT datasets along with three standard points, such as apex of bilateral mastoid process and dorsum of nose, the deviation of each POI between three CT image datasets were evaluated.

Results
For deviations of skin POIs, there were 17 POIs for deviation with over 10 mm, and 7 POIs for over 30 mm between supine position and pseudo-treatment position. In contralateral side potential to have the exit point of beam central axis, the deviations of POIs near the middle of the posterior cervical triangle had the trend to become large. The deviations in roll/pitch angles (degree) relative to skull structure due to change of position into pseudo-sitting were -10.7 ± 3.2 and -15.1 ± 9.3, compared with a supine position.

Conclusion
Our results revealed that it is inevitable to perform re-planning with CT images acquired in a sitting position as an actual treatment position because of large beam axis deviations derived from a change of patient positioning at CT imaging in head and neck BNCT.

Keyword: boron neutron capture therapy, BNCT, head and neck, preplan, position

PS1 B 01

Design of collimator for T/N-SPECT for BNCT

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For the spread of BNCT, it necessary to develop a real-time measuring instrument of the treatment effect. In our group, to solve this problem, a SPECT system so-called BNCT-SPECT is being developed, which can obtain a three dimensional image in real time by measuring 478 keV prompt gamma-rays emitted from the excited 7Li nucleus created by 10B(n, α)7Li reaction. In addition to the one described above, there are several important treatment effect indices, e.g., boron concentration, neutron flux intensity, etc. In this study, for measuring the T/N ratio, which is one of the indices, we are developing the Single Photon Emission Computed Tomography (SPECT) system for BNCT, so-called T/N-SPECT, which can continuously monitor the boron concentration three-dimensionally. We could estimate the real time differential treatment effect to tumor and normal tissues by measuring the boron concentration and the T/N ratio deduced from the measured boron concentrations. This is crucial information to decide whether to continue the neutron irradiation in BNCT.

To know the T/N ratio, we should measure 478 keV prompt gamma-rays emitted from the excited 7Li nucleus created by 10B(n, α)7Li reaction and 2.22 MeV gamma-rays emitted from 1H(n, γ)2H reaction of hydrogen contained in a human body. In the T/N-SPECT, however, this measurement should be performed in a powerful neutron background. In the measurement, the direction of these gamma-rays must thus be collimated by collimator and thereafter detected by a gamma-ray detector. Many scientists have been giving large efforts to aim at this goal, however, it is known to be very difficult, therefore, we first tried to design the collimator suitable for the present T/N-SPECT. In this study, we considered the design conditions of the T/N-SPECT collimator assuming the T/N-SPECT would be in actual treatment site. At first, we set several spatial resolutions necessary for the T/N-SPECT. Second, we changed the collimator length and diameter for each spatial resolution. Finally, we calculated the statistical accuracy of measured gamma-rays for 1 to 10 minutes, which would be acceptable update time to obtain a treatment effect image, in order finally to fix the design of the collimator. In the design, the target accuracy was set to 5 %. For the calculation, we used the three-dimensional Monte Carlo transport code MCNP5, and employed F4and F5 tallies (flux and reaction rate) and F8 tally (pulse height spectrum of gamma-rays). We assumed the size of the tumor was 3 cm in diameter, the size of the head was 20 cm in diameter, and the neutron beam was a broad beam (15 cm φ) of 10 keV. We chose GAGG(Ce) scintillator as the detecting element, considering energy resolution necessary for the T/N-SPECT and detection efficiency of 2.22 MeV gamma-rays. We tentatively decided the thickness of the detecting element to be 4 cm and the size on the front surface of the element to be equal to the collimator hole diameter. Also, to simplify the calculation, the number of holes in the collimator was set to one.
As a result of calculations, for several spatial resolutions of the T/N-SPECT, we confirmed that the collimator design could be completed for measuring time of several to 10 minutes. In the next step, we will carry out the precise design considering collimator holes bundled inducing deterioration of the shielding performance and cross-talk events between the detectors. We also plan to investigate and finally determine the size of the detection element optimal for the T/ N-SPECT.

Keyword: BNCT, SPECT, T/N ratio

Abstracts Posters

PS1 B 02

The specific retention of boric acid in liver tumor for BNCT in a single liver tumor-bearing rat and a multifocal liver tumor-bearing rabbit models

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Introduction.
Liver cancer describes a malignant hepatocellular carcinoma, which is the second most common cause of death from cancer worldwide. The prognosis for liver cancer is very poor. Most hepatoma patients are diagnosed at an advanced stage, and more than 80% of patients suffer from multifocal tumors and cannot be completely cured by surgery. To overcome such problem, boron neutron capture therapy (BNCT) may be an effective solution in liver tumor therapy. In BNCT, short ranges of two high-LET products of the boron neutron capture reaction make the specific retention of boron compound particularly important for treatment efficacy. In this study, boric acid (BA) was used as the boron drug. The specific retention of BA in the liver tumor for BNCT was investigated with two animal models of liver cancer.

Materials and Methods.
The N1S1 single liver tumor-bearing rat and the VX2 multifocal liver tumor-bearing rabbit models were established. A liver tumor-bearing rat was bolus-injected with BA (25 mg 10B/kg bw) via the tail vein, whereas the multifocal liver tumor-bearing rabbit was bolus-injected with BA (50 mg 10B/kg bw) through a marginal ear vein. Rats and rabbits were sacrificed at 30 and 35 min following the BA injection, respectively, and the tumor-bearing lobes were collected for further analyses. The boron retention in tumor-bearing liver was investigated by neutron capture autoradiography. Tumor sections with a thickness of 40 μm were prepared using a freezing microtome, and placed on a polymethyl methacrylate slide. The slide with a tumor section was directly covered with LR115 films for neutron autoradiography. The slides were placed in a polyethylene phantom and irradiated with neutrons for 30 min in Tsing Hua Open Pool Reactor. The thermal neutron flux at the exit of the beam was 1.32×109 n/cm-2 s-1. The quantitative boron distribution was evaluated by alpha track analysis using an ImageJ program.

Results.
The autoradiographic images were compared to the result of histopathological investigation to quantify the differential BA retention in the tumor and normal tissues of the tumor-bearing livers. It demonstrated that BA was selectively targeted to tumors and tumor vessels both in the N1S1 single liver tumor-bearing rat and the VX2 multifocal liver tumor-bearing rabbit. The images indicated that the track density in the tumor region exceeded that in the normal liver tissue; moreover, blood vessels in the tumor region were associated with a high density of alpha tracks. Specifically, the ratio of track density in the tumor and tumor vessels to that in the adjacent normal liver tissue was 2.5±0.5. The active regions of the tumor had a higher track density than the central necrotic area of the tumor. Neutron capture autoradiography demonstrated that the interior portions of blood vessels that surround the tumor exhibited uniformly distributed alpha-tracks with high density. Histopathological examination revealed the radiation damage to the tumor-bearing liver was concentrated in the tumor regions during BNCT treatment.

Conclusion.
BA as an adequate choice of boron drugs for BNCT for liver cancer can be specifically retained in the liver tumor area, including liver tumor cells and tumor blood vessels. The selective killing of tumor cells and the destruction of the blood vessels in tumor masses may be responsible for the effectiveness of BA-mediated BNCT for liver tumors in the animal models.

Keyword: Boron Neutron Capture Therapy, Boric acid, Specific retention, Liver tumor, Autoradiographic images, Histopathological examination

Abstracts Posters

PS1 B 03

Simulations of an imaging system based on a CZT photon detector for a future BNCT-SPECT.

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Introduction

BNCT treatment effectiveness strongly depends on the radiation dose deposited locally by the 10B(n, α)7Li reaction in the tumour, therefore the real time measurement of this quantity is fundamental to improve BNCT treatments.

To evaluate the deposited dose in the tumour it is necessary to have a correct knowledge of the 10B spatial distribution and of the thermal neutron flux in the tissue at the irradiation time. To such purpose it is possible to exploit the 478 keV dis-excitation photons of the 7Li emitted in the 94% of the cases during the boron capture reaction. Our project aims to develop a SPECT system based on a CdZnTe (CZT) semiconductor detector to be installed at a new BNCT clinical facility. The CZT detector has been characterized and its response to the neutron and gamma background in the treatment room was studied. Next step of the BNCT-SPECT projects requiers to study the imaging capabilities of the system such as the spatial resolution and the efficiency of the detection system. In the present work we studied a 20x20x20 mm3 CZT detector that can be considered as a base sensitive elemen of the BNCT-SPECT system. We studied the performances of such detector when employed as a SPECT imager. Moreover we studied a collimation system for the detector. We also studied the possibility to use the CZT detector as a Compton Camera. The main advantage of such approach would be the possibility to use the compton scattering instead of the photoelectric effect, due to the higher cross section of the first process in the CZT detector for the energy of our interest.

Materials and Methods

This study was carried out from a computational point of view using different Monte Carlo codes, in particular MCNP6 and Geant4. At first a 20x20x20 mm3 CZT detector was simulated as part of a SPECT imaging system by rotating the detector around a small animal phantom. The detector imaging capabilities were studied with a virtual collimator in three different cases: with only the source emitting the 478 keV photon, when the phantom acted as a scatterer and when the phantom was also emitting background photons. To consider a more realistic case the virtual collimator was replaced by a pinhole collimator at first and a parallel collimator in the second case. The spatial resolution of the system was studied in all the cases. Preliminary studies of the performances of the detector as a Compton camera were also carried out.

Results

The CZT detector was simulated both as SPECT imager and as a Compton camera, the spatial resolution of the reconstructed images was studied in both cases. For the CZT based BNCT-SPECT system different cases were taken into account. At first an ideal case with a tumour emitting 478 keV was studied, then more realistic cases with a scatterer phantom and an emitting phantom were taken into account. The ideal case was also used as a reference for the study of a realistic collimation system. The performances of a pinhole collimator and of a parallel hole collimator were studied.

Conclusions

The computational study of the CZT detector as a SPECT imager using a real collimation system showed that the spatial resolution of the detector is suitable for an application in clinical BNCT. The preliminary study of the CZT detector as a Compton camera showed that with further studies it would be possible to choose such application to reconstruct the image of the patient during the treatment.

Keyword: BNCT-SPECT, Imaging, CZT, Compton camera

PS1 B 04

Preliminary performance studies of a CZT photon detector using a highly thermalized neutron beam.

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Abstracts Posters

Introduction
Cadmium-Zinc-Telluride (CZT) detectors are under evaluation as photon sensors for a BNCT-dedicated SPECT system (BNCT-SPECT) by the Pavia BNCT group.
Preliminary characterisations performed inside the thermal column of the Pavia research nuclear reactor confirmed the good energy resolution of a small CZT prototype, in particular its capability to discriminate the 478 keV peak of B-10 captures from the 558 and 651 keV gamma rays emitted after the thermal neutron activation of Cd-113 inside the detector itself.
Due to the unavoidable presence of some amounts of B-10 inside the thermal column structure, the performance of the CZT detector in discriminating the signal of B-10 enriched small samples from the facility background was not completely satisfactory. As consequence, the aim of the present work is to evaluate the CZT spectroscopy for BNCT-SPECT exploiting the highly thermalized neutron beam recently open at the Pavia nuclear reactor laboratory within the project of a Prompt Gamma Neutron Activation Analysis facility (PGNAA) for archeometric and biological samples irradiation.

Materials and Methods
The present work includes both MCNP6 simulations and experimental measurements at the new PGNAA facility of Pavia reactor.
MCNP6 code has been used to simulate the neutron and gamma background affecting the region around the irradiated samples to confirm the expected collimation of the thermal beam and the low contamination of gamma rays. These features are important to optimise the measuring campaign with the CZT, in particular to minimise the neutron activation of the detector and to assure the highest possible S/N ratio around the 478 keV peak. Moreover, these calculations were used to design a preliminary shield and collimation system for the CZT detector.
Once the best measuring position has been selected by Monte Carlo calculations, a 5x5x20 mm^3 CZT photon detector was used to record the 478 keV gamma ray spectra coming from small vials containing B-10 enriched solutions of BPA, BSH or boric acid, initially in an “unperturbed” condition, i.e. without the presence of a tissue equivalent phantom. In a second phase the vials were inserted in small phantoms to study the effects on the 478 keV peak due to the scattering and attenuation introduced by the tissue equivalent material.

Results
The spectra measured by the 5x5x20 mm^3 CZT photon detector at the Pavia PGNAA facility were simulated and the different components, in particular background versus the 478 keV sample signal versus the thermal neutron activation of Cd-113, were individually studied. This brought to the identification of the best measuring position inside the PGNAA facility as well as to the requirement for a neutron+ gamma shield.
The simulated spectra were compared to the measured ones, considering several irradiation conditions going from the unperturbed one (B-10 enriched vials alone) up to more realistic ones (presence of a scattering and attenuating phantom) confirming the capabilities of the CZT detector to discriminate the 478 keV BNCT signal even in presence of a neutron+gamma background.

Conclusions
The performances of a small CZT crystal as photon detector for a BNCT-SPECT system have been evaluated in term of spectroscopy both by Monte Carlo simulations and experimental tests exploiting a highly thermalized neutron beam. The results indicate that the CZT semiconductor is feasible for the real time 10B dose monitoring in BNCT.

Keyword: BNCT-SPECT, 478 keV spectrometry, CZT detector

PS1 B 05

High performance 3D CZT spectro-imager for BNCT-SPECT: preliminary characterization.

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Introduction
The INFN 3CaTS project (High performance 3D Cadmium-Zinc-Telluride spectro-imager for X and gamma ray applications) is presently carried out at Pavia University and Pavia INFN Unit in collaboration with Palermo University, the OAS Bologna of the Italian National Institute of Astrophysics (INAF), the Institute of Materials for Electronics and Magnetism (IMEM) in Parma of Italian Research National Council (CNR) and the start-up due2lab s.r.l. in Parma, Italy.
The aim of the project is to develop an innovative room temperature highly segmented prototype of a CdZnTe (CZT) detector and to evaluate its performance as spectrometer with 3D spatial resolution capabilities suitable for different spectroscopic and imaging applications in the range from few tens of keV up to 1 MeV. The real time B-10 therapeutic dose monitoring in BNCT is included in the named applications.

Materials and Methods
A single CZT prototype with a sensitive volume of 20x20x5 mm^3 is the goal of 3CaTS project. The capability of recording in 3D the point of interaction of the incident photons is allowed by the deposition of strip electrodes on the largest detector surfaces along orthogonal directions (x-y event identification), while the third coordinate is derived by the Depth Of Interaction (DOI) analysis, based on the ratio between the electric signals induced on the anode and the cathode electrodes. The prototype is coupled with a custom digital multichannel electronics, based on two pipelined fast and slow analysis, able to perform multi-parallel analysis (event arrival time, pulse shape, pulse height) and fine temporal coincidences.

The system has been tested at the Pavia nuclear reactor laboratory for BNCT-SPECT purposes, in particular irradiating B10-enriched samples with the highly thermalized neutron beam recently developed for a Prompt Gamma Neutron Activation Analysis (PGNAA) facility as well as using point-like gamma sources or small volume neutron activated detectors.

Results
The 3D highly segmented CZT prototype developed by the INFN 3CaTS project has been tested and proved to be suitable as sensitive unit of a future BNCT-SPECT system. In particular the energy resolution at 478 keV compares very well with the expected results of less than 3%.

Conclusions
The aim of the 3CaTS project has been positively reached, i.e. the development of a 3D CZT photon detector for BNCT-SPECT. The prototype resulted to be compliant with the requirements for an effective application in BNCT, in particular in term of energy resolution considering the broad energy, mixed radiation field where the detector shall work.

Keyword: BNCT-SPECT, CZT detector, 3D spectro-imager

PS1 P 01

Feasibility study of using IRT-T research reactor for BNCT applications

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Introduction
Boron neutron capture therapy (BNCT) is a binary form of radiation therapy, which delivers the high linear energy transfer particles to tumor cells preferably without severe damage to surrounding normal tissue. Now a significant step towards implementation of BNCT as a clinical modality is extending its application to various types of cancer. Therefore, the development of new boron compounds synthesis, delivery, and evaluation is one of the most important issues that should be resolved. For the purpose of preclinical BNCT research, a project of new irradiation facility at IRT-T reactor is under development.

Materials and methods
IRT-T Research Reactor is a 6 MW pool-type reactor. Each fuel assembly contains 6 or 8 fuel tubes, which consist of UO2–Al fuel in aluminum cladding. The reflector consists of beryllium blocks. The reactor has 10 horizontal experimental channels, two of which are tangential to the core (HEC 1 and HEC-4), a beryllium thermal column, and 14 vertical irradiation channels in the reflector. Experimental channels are used for neutron activation analysis; technetium-99m radiopharmaceuticals production; irradiation of semiprecious stones and etc. Growing interest in BNCT in Russian Federation together with IRT-T reactor research capabilities have resulted the start of the project on experimental irradiation facility for pre-clinical BNCT research.
MCU-PTR code was chosen for the purpose of IRT-T reactor simulation. This code uses Monte-Carlo method and is oriented on the calculations for pool-type research reactors. The detailed geometrical model of the IRT-T reactor including fuel assemblies, reflector

blocks, control rods, main structural components, horizontal beam tubes and vertical irradiation channels was developed. Calculations of beam parameters were performed for all horizontal channels, except HEC-4, which is reserved for neutron transmutation doping (NTD) of large silicon ingots. Neutron/photon energy spectrums and three-group neutron fluxes (thermal E<0.5 eV, epithermal 0.5 eV <E<10 keV, fast E>10 keV) were calculated for available horizontal experimental channels. Fast neutrons and photons dose rates were obtained by using ICRP 21 flux-to-dose rate conversion factors.
Experiential results of neutron spectra determination was obtained by multi-foil activation method. Ni, Ti, Nb, Al, In foils was used as fast neutron detectors and Lu, Au, Cu foils was used as thermal neutron detectors.

Result
Experimental and calculated neutron and photon spectra, neutron and photon dose rate was obtained. Calculated three-group neutron fluxes for HEC-1 (in n/cm2/s) was 8.41E+08, 1.07E+08, 1.28E+08 for thermal, epithermal and fast neutron respectively. For radial channels average fluxes (in n/cm2/s) was 2.76E+09, 1.14E+09 and 2.52E+09 n/cm2/s for thermal, epithermal and fast neutron respectively. Calculation time was chosen based on relative errors: for thermal and epithermal neutrons to be less than 5 %, for fast neutrons and photons to be less than 20 %.

Conclusion
There is no significant difference between neutron/photon energy spectrums at radial beam ports. Radial horizontal channels cannot provide an appropriate neutron beam for BNCT applications due to the high contamination of fast neutrons and gamma irradiation. The absolute values of thermal and epithermal neutron fluxes in the tangential horizontal channel HEC-1 are lower compared to the radial beam ports due to the long distance (350 cm) between reactor core and channel exit. Beam quality is not enough for use in BNCT research, but with designed neutron scatter and an appropriate Beam Shaping Assembly (BSA) in the channel, it can be used for pre-clinical BNCT research. The current rotating beam shutter at HEC-1 is 1850 mm in length and its material composition consists of boron carbide, paraffin and stainless steel. Replacement of the current shutter with more compact one will allow reducing the distance between neutron source and irradiated object.

Keyword: BNCT, IRT-T reactor, Monte Carlo calculations

PS1 P 02

Data processing automatization and improvements of D-Pace OWS-30 wire scanner

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Introduction
A source of epithermal neutrons based on vacuum-insulated tandem accelerator and a lithium target was proposed and developed for the technique of boron neutron capture therapy. A stationary proton beam of 2 MeV with a current of up to 6 mA was obtained in the accelerator. It was found that increasing of the negative hydrogen ions beam current injected into the accelerator leads to the need to change the lens focusing force, increasing the frequency of breakdowns and heating of the electrode diaphragms. For the beam diagnostics, a wire scanner OWS-30 (D-Pace, Canada) was installed.

Materials and Methods
The work was carried out on an accelerating neutron source created at the Budker Institute of Nuclear Physics. The wire scanner was installed to the vacuum camera in front of accelerator inlet. The scanner has two wires fixed to a common rod. When the rod moves, the current on the wires and the rod angle are measured, which makes it possible to reconstruct the transverse profile of the ion beam along two perpendicular directions. We have modernized the scanner by placing the metal rings in front and behind the scanner with a negative potential to suppress the secondary emission of electrons from the scanner wires. We are the first who proposed and implemented a new way of measurement of the beam emittance. A movable diaphragm was inserted in front of the wire scanner. Ion beam passing through the aperture of the diaphragm was measured with a high quality detalization when the diaphragm was moved along one radius. We have developed a software in which methods for calculating the position and size of the beam, methods for calculating the total current are implemented. The software is developed using the Qt 5.8 framework. in C++.

Results
Modernization of the scanner has made it possible to expand its capabilities. The suppression of the secondary electron emission made it possible to reconstruct the current profile of the ion beam and determine the value of the total current. The use of a movable diaphragm made it possible to measure the phase portrait of the beam in two planes with

a high quality detalization. The developed program allowed to display the coordinates of the beam, its dimensions and the total current. The use of a modernized scanner made it possible to detect the effect of space charge and the effect of spherical aberration of focusing magnetic lenses on a beam of negative hydrogen ions.

Conclusion
The OWS-30 wire scanner was upgraded to suppress secondary electron emission. For the first time, a new method for measuring the phase portrait of an ion beam was proposed and implemented. A diaphragm was introduced into the beam in front of the wire scanner and the profile of the passed beam was measured. Methods for calculating the position, dimensions of the beam and calculating the total current, are proposed and developed. Software for displaying beam parameters has been developed. The use of the modernized scanner made it possible to optimize the injection of a beam of negative hydrogen ions into the accelerator, which led to an increasing in the proton current and an improvement of the accelerator stability. The modernized scanner with an additional program for processing the results data and visualization has become a reliable device for beam diagnosing and for controlling its entry into the accelerator.

Keyword: vacuum-insulated tandem accelerator, BNCT, profilometer

PS1 P 03

Visualization of a negative hydrogen ions beam in a vacuum insulation tandem accelerator

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Introduction
A source of epithermal neutrons based on vacuum-insulated tandem accelerator and a lithium target was proposed and developed for the technique of boron neutron capture therapy. A stationary proton beam of 2 MeV with a current of up to 6 mA was obtained in the accelerator. High acceleration rate (up to 25 kV/cm) and a strong input electrostatic lens that determines the trajectory of the ion beam and the heating of the accelerator elements characterize the accelerator. It was necessary to develop a diagnosis of the position of the beam and its size in the accelerator for optimal beam injection into the accelerating channels.

Materials and Methods
The work was carried out on an accelerating neutron source created at the Budker Institute of Nuclear Physics. It is proposed to detect the optical radiation produced by the interaction of ions with the residual and stripping gas. To convert negative hydrogen ions into protons a stripping target with argon gas is used. Registration of optical radiation is carried out by two network cameras DS-2CD4025FWD-A of Hikvision, aimed from above and from the side to the diaphragm of the first intermediate electrode providing a potential of 160 kV. A software was developed that connects to cameras, calculates position and beam dimensions and stores these parameters in a local database. The program was developed using the Qt 5.8 framework in C++.

Results
On the video image from the cameras, the luminescence due to the interaction of the accelerated ions with the residual and stripping gas was clearly recorded. Software was developed that processes frames from both cameras and displays information about the position and size of the glowing area in real time. The use of the developed diagnostics made it possible to control the ion beam along the axis of the accelerator with the use of correctors installed in transportation path. The use of the developed diagnostics made it possible to explore the effect of a magnetic focusing lens installed in the transportation path of negative hydrogen ions beam and the effect of the potential of the first accelerating electrode on the beam size. Optimization of ion beam injection into the accelerator allowed increasing the proton beam current up to 6.7 mA and increasing the stability of the accelerator.

Conclusion
Optical diagnostics has been developed and introduced, which makes it possible to monitor the position and size of the ion beam accelerated in a vacuum-insulated tandem accelerator. The use of diagnostics made it possible to optimize the injection of a negative hydrogen ions beam into the accelerator, improve the stability of the accelerator and increase the proton current.

Keyword: vacuum-insulated tandem accelerator, BNCT

Abstracts Posters

PS1 P 04

Optimization of the beam shaping assembly and local protection of the accelerator source of epithermal neutrons

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Introduction

Boron Neutron-Capture Therapy (BNCT) holds much promise for cancer treatment through the selective destruction of tumor cells which first accumulate the stable nonradioactive isotope 10B and are then irradiated by neutrons. Intense fluxes of epithermal neutrons, or neutrons with energies between 1 and 30 keV, are needed for this purpose. The best way of generating such neutrons is the reaction 7Li(p, n)7Be that yields a quite large number of neutrons with the softest energy spectrum. The neutrons are moderated to required energies in a Beam Shaping Assembly (BSA) which includes a moderator, a reflector, an absorber, and, in some cases, a filter.

Materials and Methods

Proton, neutron, and gamma transport was simulated by the Monte Carlo method with the use of a PRIZMA code and the ENDF/B-VII library of data on neutron and gamma interaction with matter. Data on neutron production in the reaction 7Li(p, n)7Be and high-energy gamma production in the reaction 7Li(p, γ)8Be → 2α were taken from a nuclear physics data handbook and data on the gamma-generating reaction 7Li(p, p)7(1*)Li were prepared on the basis of the EXFOR database. The BSA is described in detail in accordance with the drawings; the silo and the main elements of the accelerator are presented by simple figures with mass and composition conservation. The deep distribution of doses was calculated in the modified Snider phantom with the concentration of 10B set to be 15 ppm in healthy tissue and 52.5 ppm in tumor. The spatial dose rate distribution outside the silo was determined on a fictitious screen one meter from its wall.

Results

We considered several BSA versions which differed in size and composition. The best of them is the version with a composite moderator consisting of magnesium fluoride (closer to the target) and aluminum fluoride (closer to the outlet). The graphite reflector in the forward hemisphere helps attain much higher doses in tumors which seat at depths up to 6 cm. For deeper tumors, the dose can be increased with the use of a lead reflector. We propose employing a proton beam of energy 2.3 MeV which is close to the energy at which the reaction cross section reaches a maximum. The use of higher energy protons can only be justified for tumors which seat deeper than 7 cm. The optimized BSA is manufactured; it produces proton beams that to a great extent meet BNCT requirements. We considered several versions of local protection. It is found that the best solution is to place borated polyethylene on the inside of the silo's door. This allows us to meet the radiation safety standards and generate neutrons for a long time.

Conclusion

A BSA consisting of a moderator, a reflector, and an absorber is used to generate neutron beams for BNCT. For the first time we propose here employing a composite moderator formed by magnesium fluoride near the neutron-producing target and aluminum fluoride near the outlet along with a composite reflector with graphite in the forward hemisphere and lead in the backward hemisphere and generating neutrons via the reaction 7Li(p, n)7Be induced by 2.3-MeV protons. Through numerical simulation of neutron and gamma transport we have shown that the proposed solutions make it possible to shape a therapeutic neutron beam which to a great extent meets BNCT requirements.

Keyword: BNCT, BSA

PS1 B 06

PGNAA facility at RA-3: numerical approach towards first measurements of biological samples for BNCT

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A Prompt Gamma Neutron Activation Analysis (PGNAA) facility is being developed and constructed in the Channel 4 of RA-3 fission nuclear reactor by the Argentine National Atomic Energy Commission (CNEA). Such technique provides the possibility of measuring 10B concentrations in biological samples for different BNCT activities. The aim of this development is being able to measure micrograms of 10B in a few minutes of irradiation, conditions that are very important for research, development and specifically for clinical assessments.

After iterative process of simulation guided design, construction and experimental measurements, a beam with high thermal neutron flux and very low epithermal and fast components has been achieved at the sample position. After reaching that goal, the detector region was modified in order to reduce the gamma background as low as possible. In an intermediate stage of the modifications, measurements of tens of micrograms of enriched boron powder, could be clearly identified at the HPGe detector, which agreed with previous simulations. Knowing that boron could be detected, it was needed to study how biological tissues in the sample holder would affect the measurements, simulations of different amounts of blood and blood with different concentrations of 10B have been performed with MCNP code. The assessment of the results was mainly dedicated to the detection limit of the facility, where the last modifications are being implemented and will be assessed.

The current design of the PGNAA facility, has been tested for biological samples by performing simulations. Volumes of blood samples have been studied between 10 and 1000 µl for different 10B concentrations. The lowest detection limit achieved was about 3 ppm in 1.0 ml and 15 ppm in 0.1 ml, of 10B concentrations and blood sample volumes respectively. Volumes of 1.0 ml 0.1 ml blood samples increased the gamma background up to about 3.7 and 2.7 times, compared to the sample holder without sample. Measurements with prepared equivalent patterns need to be performed in order to confirm the calculations.

We are developing a PGNAA facility that is close to its desired minimum detection limit of 0.1 µg. Without reaching to the final goal, at this stage, the simulations showed that would be possible to measure boron concentrations above 3 ppm in 1.0 ml of blood samples with the current design. Modifications of PGNAA facility are being proposed, simulated and assessed in order to keep improving the boron detection limit. This will be complemented by experimental work with the implemented modifications on the facility.

Keyword: Prompt gamma, boron measurement, spectrometry, MCNP, biological sample

Group II

PS1 P 05

Study of the potential application of low energy neutrons from neutron guides to BNCT radiosurgery

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Introduction

Low energy neutrons, from thermal to cold, can be guided and focused, not only for obtaining pure neutron beams like PF1b at ILL or the ANNI beam line proposed for ESS, but also for producing neutron beams at the millimeter o even micrometer scale. In previous meetings it has been raised the possibility of using such beams by inserting the guide into the patient. For the evaluation of this option, a dosimetric study is mandatory.

Materials and Methods

Monte Carlo calculations of the dose delivered in a standard tissue in the vicinity of the exit of a neutron guide have been performed for different neutron wavelengths. The neutrons are transported by means of calculations with FDTD and McStas. The RBE and boron concentrations, both at tumor and normal tissue, have been taken as the standard values used in the literature.

Results

Depth dose profiles and lateral dose distributions will be shown. It will be observed a very important enhancement of the dose absorbed by the tumor (more than 5 times the boron dose, in comparison with dose received by healthy tissues) in a very local volume near the exit guide. There is a dependence of this volume with respect to the neutron energy.

Conclusion

These results suggest the possibility of applying neutron guides to treat internally the surrounding tissue after resection of a tumor, but more research is required in order to determine a practical use.

Keyword: BNCT, cold neutrons, thermal neutrons, neutron guide, Monte Carlo simulations

Abstracts Posters

PS1 P 06

Neutron control method for an accelerator-based BNCT system with a solid-state Li target

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Introduction:
A solid-state Li target is one of options for accelerator-based BNCT system. However, there are some difficulties. One of them is large thermal loads to the Li target. Previous study suggested that the number of generated neutrons per an irradiated proton to the Li target might decrease with depending on cumulative proton irradiations to the Li target because of decreasing thickness of the Li target. Purpose of this study is to establish a control method for the number of irradiated neutrons under a clinical situation, using the number of irradiated protons to the Li target and a prediction model for the decreasing.

Materials and Methods:
Experiment was performed with the accelerator-based BNCT system with a solid-state Li target (Cancer Care Intelligence Systems, Tokyo, Japan) in NCCH. There were two processes in this study. In the first process, the saturated radioactivity of gold wires which were placed on the surface of an irradiation port in the accelerator-based BNCT system was evaluated several times at each cumulative proton irradiation to the Li target in order to establish the prediction model. Saturated radioactivity of the gold was used for surrogate of a neutron flux, and was evaluated as variables of amounts of the protons to control the number of the irradiated neutrons with the number of the irradiated protons to the Li target. The prediction model for the variables was established as a function of the cumulative proton irradiation to the Li target, using all of the measured variables. Discrepancies between the measured variables and the predicted variables were evaluated. In the last process, the number of neutrons which was required in a treatment of BNCT was controlled by the prediction model and the number of the irradiated protons to the Li target. Treatment time of BNCT was assumed as 2 hour in this study, and integral quantity of the neutron flux during the treatment was calculated with the function of the prediction model. The prediction model was established every measurements of the saturated radioactivity with using the measured variables from the first to the last measurement, and then, the calculated integral quantity was evaluated at each of the measurements. The other prediction model which was determined in the first process was used to calculate measured integral quantities of the neutron flux during the BNCT treatment. Discrepancies between the measured integral quantities and the calculated integral quantities were evaluated. Five of the Li targets were examined whether the prediction model and the calculated integral quantity could be applied to the neutron control which had sufficient accuracy for treatment.

Results:
In the first process, the discrepancies for the variables in the five Li targets showed the normal distribution ($p = 0.60$, 0.89, 0.89, 0.50, and 0.62). Mean difference and standard deveiations (SD) in each of the Li targets were (0.0±1.1)%, (0.0±1.0)%, (0.0±1.2)%, (0.0±1.2)%, and (0.0±1.6)% (mean±SD). Thus, the decrement of the generated neutrons might be adequately represented by the prediction model. In the last process, mean±SD in the integral quantity of each Li target were (-0.2±1.2)%, (0.0±0.7)%, (0.0±0.8)%, (-0.3±0.9)%, and (-0.4±1.6)%. Therefore, it was suggested that pre-determined neutron fluence could be irradiated within almost 1-2% in the accelerator-based BNCT system, using the number of irradiated protons to the Li target and the prediction model.

Conclusion:
This study demonstrated an accuracy of the control method using amounts of proton irradiations to a target system in an accelerator-based BNCT system with a solid-state Li. Amounts of therapeutic radiation in the accelerator-based BNCT system with the solid-state Li target can be controlled with adequate accuracy comparative to common radiotherapies such as using photons and electrons.

Keyword: Accelerator-based BNCT system, neutron control

Abstracts Posters

PS1 P 07

A High Flux Thermal Neutron Source for Small Animal Models for the Development of Drugs for Boron Delivery to Cancer Sites

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A high flux neutron source (model DD110.8MB) with an integral moderator and small-animal-model (e.g. mouse) chamber has been designed, fabricated and installed at the Fukushima SiC Applied Engineering (FSiC) Laboratory at its Naraha Facility in Fukushima Japan. The moderator has been designed to produce an optimized thermal flux of neutrons obtained from four, high-yield, DD-fusion generators. Early measurements of the neutron yield and flux have been performed.

Previously, DD fusion reaction generators have had low fast neutron yields and were not moderated for high fluxes of thermal neutrons. The moderator has a central chamber wherein the small animal model can be inserted and quickly removed. The moderator uses high density polyethylene (HDPE) and heavy water (D2O) to moderate the 2.5 MeV fast neutrons coming from the four DD-fusion generators. The generators are arranged concentrically around the moderator and its central chamber. This maximizes the thermal flux at the chamber while also reducing the unwanted components of x-ray, gamma and fast neutrons.

Its maximum fast neutron (2.5 MeV) yield has been measured to be 8 x 10^10 n/sec, while it's thermal (< 0.5 eV) flux is expected to be 2.6 x 10^7 n/cm2sec. Higher yields were obtained by increasing the acceleration voltage to 225 kV. The total supplied power is approximately 20 KW and the four generators plus moderator is enclosed in a 3.1 x 3.1 x 1.3 m shielded box; thus, such system is easily installed in small laboratories.

The model DD110.8MB neutron system provides us a tool to improve and benchmark our designs for clinical systems, and proves the feasibility of running multiple neutron generators heads from one control system and power supply rack. Compared to some other methods of producing neutrons, our source 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 generators are designed to have a long life, and have 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. Higher yields and fluxes can be achieved using the model DD110.8MB by adding more single beam generators and increasing the acceleration voltage.

Keyword: small animal testing, neutron source, boron delivery

PS1 P 08

Neutron Beams Optimization of Nuclear Medical Ship

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From a consideration that most large and medium sized research reactors used for BNCT have been decommissioned in concomitance with their life span termination or closed down due to the aging facilities, an ocean-going nuclear medical ship (NMS) design has been started since 2010 while done and demonstrated in 17th ICNCT, 2016. The NMS named "Star of Hope" is aimed to treat breast cancer in no-nuclear countries and areas with diagnosis and clinical trial facilities of neutron capture therapy (NCT) as well as conventional radiation therapy (CRT). The NCT system is based on a set of miniature nuclear reactor neutron source called Cancericidal Nuclide Neutron Knife (CNNK), with an epithermal beam and a mixed beam. Unfortunately, the neutron flux of this epithermal beam is not high enough for quick and effective irradiation. Optimization and modification has been done to improve epithermal neutron flux and harden neutron spectrum.

Simulations of the reactor source combining various materials and geometries have been calculated. The marginal circle of fuel rods is removed, with thickened beryllium reflector instead. A square cutting of aluminum replaces part of the beryllium reflector towards the epithermal beam. With an increased Hydrogen-Uranium rate and weaken reflector, the epithermal neutron flux can be enhanced to 8.1E+08n·cm-2·s-1 at the port. The mixed beam has also been modified to provide a thermal neutron flux of 1.0E+09n·cm-2·s-1 and an epithermal neutron flux of 2.0E+08n·cm-2·s-1.

Keyword: epithermal beam, neutron source, nuclear medical ship

Abstracts Posters

PS1 P 09

Calculation of the response matrix of a PMMA cylindrical neutron spectrometer in consideration of angle distribution

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Introduction: The multi-sphere neutron spectrometer, known as a Bonner sphere spectrometer (BSS) has been widely used to evaluate the neutron spectra by the unfolding method. The measurement principle is to use a thermal neutron detector and surround them by neutron moderators of varying thickness. This kind of neutron spectrometer need to calculate the detector response as a function of the neutron energy for every size of the sphere respectively. The detector response, called a response function, is influenced by the materials, thickness and density of the moderator. Generally, as the moderator thickness increased, the detector response peak tended to higher neutron energy. In this study, we propose an Optical Fiber (SOF) detector-based neutron spectrometer associate with a polymethyl methacrylate (PMMA) cylindrical moderator. In order to evaluate the cylindrical design the SOF detector-based neutron spectrometer, we carried out the Monte Carlo simulation. This simulation results showed that the cylindrical design was more influenced by the angular distribution of neutron beam than the sphere type moderator. To overcome this issue, we analyzed the double-differential neutron yields (DDNYs) from beryllium target irradiated by deuteron and calculated the response functions which considered the beam angular distribution of neutron source.

Materials and Methods: The Monte Carlo particle transport simulation code, Particle and Heavy Ion Transport code System (PHITS) version 2.8.1, was used to estimate the response function. The presented spectrometer modeled as a 300 mm-length by 100 mm-diameter cylinder made of a PMMA with SOF detectors array placed on the central axis in the cylinder from one of the circular faces (0 mm) to 290 mm in 10 mm increments. The SOF detector consists of a miniature plastic scintillator contained LiF powder (enriched 95% 6Li) mounted on a plastic optical fiber. This probe was modeled as 1 mm-diameter optical fiber with 2.2 mm-diameter black polyethylene optical shielding. The response function was evaluated as the 6Li(n, alpha)3H reaction rate for each incident neutron energy between 1 meV and 20 MeV. In order to estimate the beam angular distribution of accelerator-based neutron source, the DDNYs from the 9Be(d, n) reactions were calculated by using the PHITS simulation. After that, the response functions which considered the beam angular distribution were calculated. The numerical simulation was carried out to evaluate the difference of unfolded results between one which used the angular differential response matrix and the other which used the response matrix calculated by a broad parallel beam from the surface of a disk shape source. The neutron spectra were estimated from the unfolding technique using the MLEM (Maximum-Likelihood Estimation Maximization) iterative method.

Results: The unfolded result which calculated using angular differential response matrix was in good agreement with the true neutron spectra produced by deuteron bombardment of beryllium target. On the other hand, the unfolded result which calculated using the parallel beam response matrix resulted in the underestimation of neutron spectra especially fast energy region.

Conclusion: The response matrix of spectrometer which composed of a PMMA cylindrical moderator with a number of the SOF detectors for accelerator-based neutron source from the 9Be(d, n) reactions was estimated by using the PHITS simulation. For the cylindrical design, it was suggested that considering the angular distribution of neutron beam is necessary.

Keywords:Neutron spectrometer, Monte Carlo, Double-differential neutron yields

PS1 P 10

Investigation of 124Sb-Be neutron source for BNCT.

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<Introduction>

As third neutron source, following reactors and accelerators, isotopes have advantages such as stability of the neutron production and ease in controlling. Among them, the combination of gamma ray source 124Sb and 9Be target produces neutrons with about 24 keV, close to the upper limit of the epithermal region. This 124Sb-Be source may make it possible to control on-off of the neutron production by adjusting the distance between 124Sb and Be. This study investigates the usage of 124Sb-Be neutron source for boron neutron capture therapy.

<Materials and Methods>
The neutron yield was calculated using Monte Carlo calculations with the PHITS code. Be was set with varied thickness around 124Sb. The energy spectra for neutrons and gamma rays were tallied and tissue kerma in air was estimated. Through this, the required activity was also estimated for a standard of beam quality as an epithermal neutron beam by IAEA-tecdoc-1223.

<Results>
For an apithermal neutron beam, Be with the thickness of about 13 mm is required. In this case, the required activity is in the order of ten to the fifteenth Bequrel. In this case, the contamination of gamma rays is about four orders higher than the standard. By combining 30 cm thick Bi, the beam quality satisfies the satandard. In this case, the required activity is about ten to the seventeenth Bequrell.

<Conclusion>
An example of the required activity of 124Sb was estimated for the 124Sb-Be neutron source in a very simple configuration of the moderator assembly. The designing of the moderator assembly which reduces the required activity will be the key-factor in realizing the usage of 124Sb-Be source in BNCT.

Keyword: Neutron source, isotope

PS1 P 11

Investigation of beam component monitor for BNCT using gel detector

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<Introduction>
A way of the quality assurance and quality control for boron neutron capture therapy (BNCT) is the measurement of the spatial distributions of the beam components is. 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.

<Materials and Methods>
The enegy 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 6Li. The beam of 10X10 cm2 was assumed to be impinged on the gel cylinder of 20 cm in diameter and 20 cm in length. The concentration of 6Li suitable to separate the beam components was investigated. Also, the condition to estimate the intensity of the epithermal neutron component was investigated for 33S as a converter.

<Results>
For the usage to monitor along the gel surface, the contribution to the total energy deposition in the gel without 6Li was 10-30 % for fast neutrons, 80-85 % for epithermal neutrons at depths over 4 cm, below 3 % for the others. For 6Li 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 6Li, the epithermal neutron contribution was over 90 %. This suggests the epithermal and fast neutron components are possibly measured by using the gel with 6Li 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 6Li. For higher 6Li concentration, the contribution of alpha and tritons increased due to increase in 6Li(n, a)3H reaction rate. At 100 ppm of 6Li, 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 6Li concentrations of 1, 10, and 100 ppm.

<Conclusion>
An example of the conditions to separate four components are shown in this study. Related findings will also be reported with respected to the usage of the gel detector for this purpose.

Keyword: QA, Gel detector

PS1 P 12

Design of a model for BSA to meet free beam parameters for a 3.5 MeV linear accelerator

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The use of accelerator as a neutron source has been the mainstay of the development of BNCT. In this study, BSA was designed for a neutron beam generated by a 3.5 MeV linear accelerator. The systematic analysis approach explores the effects of different materials and thicknesses for neutron moderation. A BSA design for lithium target was proposed in this study.
HEC Pharmaceutical Co., Ltd. cooperates with the Institute of High Energy of the Chinese Academy of Sciences to propose a 3.5 MeV linear accelerator for the accelerator-based BNCT project. In this study, AL, AlF3, PE, PbF2, TiF3, FLUENTAL, Al2O3 and MgF2 were considered as slow down material, and Bi acted as a neutron multiplication layer. Neutron yield, angular distribution, and energy distribution of neutron beams were evaluated by different proposal. The sensitivity analysis was performed for the above materials under different structure design. The obtained BSA design was satisfied the IAEA requirements for treating neutron beams, where Φepi is 1.6x109 (epi-neutron/cm2-sec), Φth/Φepi is 0.01, J/Φepi is 0.82, Df/Φepi is 3.57x10-14 (Gy-cm2/epi-neutron), and Dγ/Φepi is 7.25x10-14 (Gy-cm2/epi-neutron). Proton beam intensity requirement is 10 mA.
In this study, we perform the BSA design for a 3.5 MeV linear accelerator. The IAEA requirements were met and patients can achieve the required dose within a reasonable time.

Keyword: BSA, linear accelerator, lithium target

PS1 P 13

Development of a treatment planning system for BNCT

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Boron Neutron Capture Therapy (BNCT) is a radiation therapy for cancer that employs a neutron beam and a 10B-loaded drug to selectively kill tumor cells whilst sparing surrounding healthy tissues. The treatment planning system is an important tool in the BNCT treatment process and can assist physicians making the decision for treatment strategy. Currently, Monte Carlo method is the calculation engine in the TPS. An appropriate user interface is used to perform pre-processing and post-processing procedure for calculation engine.
HEC Pharmaceutical cooperates with the Institute of High Energy of the Chinese Academy of Sciences for the accelerator-based BNCT project. A home-made BNCT TPS was developed for dose calculation. In the early stage, C++ was used as a program language. Patient's computer tomographic image was imported into TPS; and it was converted into the required input files for the MCNP and PHITS Monte Carlo codes. When calculation is finished, the results were imported into the TPS again; the dose result and treatment time were displayed through the TPS. In this study, the Snyder phantom was used as a research case, and the calculated results were compared with the SERA and NCTplan to ensure the correctness of the process.
In this study, both mathematical-type and voxel-based Snyder phantom were tested. The HEC-TPS consist well with SERA and NCTplan, including point dose, 2-D dose profile, and dose volume histogram. In the near future, PET imaging fusion, multi-plan comparison, and patient dose correction (planQA) functions will be added, which make our TPS friendlier for clinicians and medical physicists.

Keyword: TPS, MCNP, PHITS

PS1 P 14

Quality assurance of an accelerator-based boron neutron capture therapy system: Dosimetric and mechanical aspects based on initial experience

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Abstracts Posters

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Introduction
Quality assurance (QA) procedures are necessary for establishing safe and accurate dose delivery of any radiation therapy treatment modality including accelerator-based boron neutron capture therapy (AB-BNCT). AB-BNCT clinical trials at Southern Tohoku BNCT Research Center (STBRC) are now ongoing with the aim of acquiring approval for medical equipment from the Ministry of Health, Labor and Welfare. During clinical trials, we are performing machine QA tests prior to each treatment. However, it is expected that periodical QA procedures and program enduring utilities have to be established to manage routine clinical workflow in near future. The purpose of this study is to establish essential methodology of QA procedures for AB-BNCT system based on our initial experience.

Materials and Methods
In April 2014, AB-BNCT system with cyclotron-based epithermal neutron source (C-BENS) manufactured by Sumitomo Heavy Industries, Ltd. (SHI) was installed at STBRC. The C-BENS consists of a cyclotron accelerator which can produce more than 1 mA proton beam with an energy of 30 MeV, a beam transport system, a beryllium neutron production target, a beam shaping assembly, and a collimator assembly. Remote patient transport system (RPTS) enables the hospital staff in BNCT to work outside of the treatment room under the condition of intense remaining activities just after an irradiation. High geometrical accuracy is required for RPTS to set-up a patient from preparation room to predetermined position in treatment room.
Because no QA guidelines for AB-BNCT system are now available, the dosimetric and mechanical QA requirements for clinical use of AB-BNCT system were deliberated and rearranged as the clinical trials went on based on our experience and the QA items summarized in American Association of Physicists in Medical Task Group 142 report which is widely used and referenced for general QA tests for medical linear accelerators. Daily, monthly and annual QA procedures for AB-BNCT were proposed and those feasibilities were considered.

Results
In dosimetric QA, each QA procedure consisted of evaluation of thermal and epithermal neutrons by gold wires with or without cadmium cover, evaluation of fast neutron by indium foils, and evaluation of gamma-ray by thermoluminescence dosimeter. The use of real-time neutron detector, whose stability and durability under condition of high neutron flux has not yet been clarified, is avoided because of difficulty in operation in a hospital at present.
On a daily basis, measurement of reaction rate of gold wire at the center of field, machine safety check, x-ray alignment check, and some mechanical tests are performed. The monthly QA procedures primarily involve neutron beam quality checks, which are time consuming and cannot be performed during the daily morning QA checks. Thermal neutron and gamma-ray dose profiles are measured with water phantom and some mechanical consistency tests of RPTS are performed on a monthly basis. The annual QA is the most comprehensive of all periodic checks and includes the mechanical functionality checks of RPTS, the evaluation of quality and proper functioning of imaging devices, safety checks, and the verification of all dosimetry data including out-of-field neutron and gamma-ray measurements. The annual QA will be performed in cooperation with SHI using some weekends.

Conclusion
This methodology provides a simple and reliable QA procedure that can be clinically applied with dosimetric and mechanical validity for AB-BNCT. In AB-BNCT system, there can be unexpected changes in machine performance due to machine malfunction caused by mechanical breakdown, accidents, or component failure. Further investigations will be needed to establish simple, rapid and reproducible QA procedures.

Keyword: Boron neutron capture therapy, Accelerator, Quality assurance, Measurement

PS1 P 15

Evaluation of a newly developed water-equivalent bolus technique in accelerator-based boron neutron capture therapy for skin tumors

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Introduction:
The accelerator-based boron neutron capture therapy (AB-BNCT) system was developed in order to enable the installation of safe hospital BNCT. An important feature of AB-

BNCT system is its capability of delivering great doses to deep-seated tumors under condition in which a beryllium target and neutron-beam-sharping assembly are adjusted for production of epithermal neutron that is applicable for more types of tumor localization. Conversely, AB-BNCT is less suitable for superficial cancers, such as malignant melanoma. The aim of this study was to confirm a newly developed technique with a water-equivalent bolus as a useful method for AB-BNCT for skin tumors.

Materials and Methods:
The simulated patient with a malignant melanoma with 3-cm diameter localized lesions in a sole, an arch, and a thumb of a unilateral foot was played by a healthy man. A water-equivalent bolus was prepared as follows: Urethane foam was cut down into the size of 3-cm larger than the superficial lesion, infiltrated with distilled water with deaeration, and covered with a thin film. The lesions were bordered by a catheter and covered with a water-equivalent bolus, and CT scan was performed. Using treatment planning system SERA, the tumor is depicted as a region surrounded by the catheter with 5-mm thickness. A water-equivalent bolus was delineated as water. This was placed into air for calculation in condition with no bolus. For comparison with bolus-like effect of a covered collimator, the outline of an imaginary collimator cover was set as a mass of polycarbonate or a water tank filled with water with 5-50-mm thickness. For calculation of photon-equivalent dose (Gy-Eq), blood 10B concentrations, 10B tumor/blood concentration ration, and CBE factor for 10B(n, α)7Li reaction were assumed to be 25 ppm, 3.5, and 4.0. Irradiation condition was defined as tumor minimum dose of 30Gy-Eq. Then, treatment plans were made so that the doses of the skin were as low as possible.

Results:
In condition with no bolus, irradiation time was 185.6±56.4min, and tumor maximum dose and mean dose were 110.7±31.6 Gy-Eq, and 66.2±13.0 Gy-Eq, respectively. Skin maximum dose was larger than 15 Gy-Eq in all cases. In condition with water-equivalent bolus technique, irradiation time was 48.4±15.9 min. Tumor maximum dose and mean dose were 58.5±5.3 Gy-Eq and 48.2±4.2 Gy-Eq with good dose homogeneity and within skin tolerable dose (12.7±1.6 Gy-Eq). The bolus-like effect of covered collimator with a mass of polycarbonate or water tank was not sufficient. Dose homogeneity and irradiation time were even worse than the condition with a water-equivalent bolus.

Conclusion:
Our results revealed that the newly developed water-equivalent bolus technique could have a great effectiveness on dose improvement of AB-BNCT for skin tumors.

Keyword: accelerator-based boron neutron capture therapy, water-equivalent bolus, skin tumors

PS1 P 16

Development of Thermal Neutron Moderator for Testing Boron Agents for Boron Neutron Capture Therapy (BNCT)

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IIntroduction
Boron Neutron Capture Therapy (BNCT) is a noninvasive cancer therapy and particularly effective for head and neck, brain and skin cancers. In addition to the intensity of neutron beam, the performance of boron agents is also important to improve availability of BNCT. Accessible neutron sources are necessary to develop boron agents efficiently. We decided to develop a thermal neutron source by making a dedicated moderator at neutron exposure accelerator system for biological effect experiments (NASBEE) which already works stably.
The thermal neutron flux of 10^9 n/cm^2/s is desirable for clinical BNCT to finish treatment within several tens of minutes. In the case of cell irradiation experiments, irradiation time of more than one hour will be allowed. Therefore, flux of several times 10^8 n/cm^2/s may be sufficient. The γ ray dose rate should be below several Gy/h to avoid large biological effect in experimental results. We planned to construct a moderator fulfilling these conditions.

Materials and Methods
We designed the moderator with a Monte-Carlo simulation code of PHITS based on a nuclear data JENDL-4.0. The source particles of the simulation are neutrons whose energy and momentum distributions are generated from a calculation code based on experimental data.
The neutron yield from the target is 1.39 × 10^9 n/μC. The proton beam current was as-

sumed to be 600μA. In order to maximize the produced thermal neutron flux, we planned to fill a collimator for fast neutron extraction hole with moderator material. We compared the thermal (<0.5 eV) neutron flux and the γray dose rate for the moderator of polyethylene, beryllium, graphite and polyethylene with a lead shield. The moderator of polyethylene with a lead shield can fit the condition for irradiation experiments of the thermal neutron flux of greater than several times 10^8 n/cm^2/s and the γ ray dose rate of less than several Gy/h.
Slots for irradiation samples are necessary for a realistic moderator design. We designed moderators with nine slots for cell sample tubes. The slots are located just below the lead layer to gain maximal thermal neutrons under the lead.
We carried out the performance test of the moderator. The thermal neutron flux was measured with the gold foil activation method using foils of 2.5 × 2.5 mm with 10 μm thickness and cadmium shield with the thickness of 0.5 mm which can cover a gold foil. The radioactivity of gold foils was measured after the irradiation with a NaI scintillator and the thermal neutron flux was estimated by calculation using the radioactivity of gold foils and that covered by cadmium covers. The γray dose rates were measured by thermoluminescent dosimeters (TLDs).

Results

For the center position for irradiation experiment, the thermal flux was 2.20 × 10^8 n/cm^2/s, the cadmium ratio (the radioactivity ratio of gold foils to those covered by cadmium) was 8.90 and the γ ray dose rate was 2.12 Gy/h. The thermal neutron flux is higher for a position nearer the moderator center.

Conclusion

We constructed a thermal neutron source at NASBEE in National Institute of Radiological Science. The design of the neutron source is optimized for testing performance of boron agents for BNCT. The thermal neutron flux, cadmium ratio and γ ray dose rate for 600μA proton beam operation were measured to be 2.20 ×10^8 n/cm^2/s, 8.90 and 2.12 Gy/h, respectively. These values indicate the practicality of this source for testing boron agents.

Keyword: neutron source, boron agents, phits

PS1 P 17

Patient-Position Monitoring System for BNCT Irradiation

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INTRODUCTION: In boron neutron capture therapy (BNCT) irradiations carried out at Kyoto University Research Reactor, sitting position has been applied in many cases, considering flexibility of patient positioning and structural restriction of an irradiation facility. In some cases, there is difficulty in reproducing a patient position determined by a treatment planning process, which is related to a patient set-up error. Also, the sitting position is sometimes unstable, resulting in displacement from an initial set-up position during an irradiation period, which is related to patient motion. These set-up error and motion cause uncertainty in estimation of delivered dose.
Aiming to improve the dose estimation accuracy, we have been preparing a patient-position monitoring system using a real-time range sensing devices. An outline of the monitoring system and initial test operation are described.

MATERIALS AND METHODS: The monitoring system consists of sensor devices and an analyzer. Kinect sensor (MICROSOFT CORPORATION, USA) including a real-time range camera based on a time-of-flight method, was used to track a patient position. A range sensor of the Kinect has the following specifications: a frame rate of 30 fps and an image size of 512x424. Two Kinect sensors were placed at a distance of a few meter from a patient and viewing the patient from different directions. Data acquired with the each range camera, which is a 2D range image showing a pixel-by-pixel distance map to surface points of objects from the camera, was transferred to the position analyzer. In the analyzer, 3D surface data of a patient and surrounding objects was constructed from a set of range images, and then stored as a point cloud data represented in an arbitrarily specified Cartesian frame, such as a frame parallel and perpendicular to a beam axis.
These data can be used for patient position monitoring not only by visual observation but also by quantitative evaluation. Also, displacement due to a set-up error and motion can be evaluated by comparing a position determined in a treatment planning system with a position measured by this system.

RESULTS: An initial test operation of the Kinect sensor was conducted. The sensor was placed at a distance of 200 cm from a reference object. It was confirmed that the indi-

cation of the distance was correctly displayed. However, the observed distance showed somewhat large time fluctuation in a range of ±30 mm, which was considered as random noise. A moving averaging method was applied to reduce the fluctuation, and it was confirmed that the average over 100 frame could reduce the fluctuation to < 5 mm. Also, it was confirmed that the analyzer could calculate 3D surface data from a set of range data and display a range image with a viewing axis parallel to a beam axis.

CONCLUSION: An outline of the monitoring system and initial test operation results were described. It was confirmed that the range sensing devices used in the system have sufficient accuracy and the position analysis can be correctly performed. The system can be expected to work effectively for monitoring a patient position. Functions to calculate a displacement are needed to evaluate a set-up error and motion, and are currently under development

Keyword: patient positioning, set-up error, patient motion, Kinect

Group III

PS1 R 01

Folate-modified cyclodextrin improves the intratumoral accumulation of existing boron compounds.

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[Introduction] Boron neutron capture therapy (BNCT) is a next-generation radiation therapy that irradiates thermal neutrons to boron compounds accumulated in tumor cells and selectively irradiates tumor cells with high LET radiation by the generated α-rays and Li nuclei. The therapeutic effect of BNCT greatly depends on the boron compound which collects boron at the tumor site, and existing boron compounds, L-p-Boronophenylalanine (L-BPA) and disodium mercaptoundecahydrododecaborate (BSH) have limitation with regard to the adaptive cancer type and its sufficient and specific accumulation to tumor. Therefore, new boron compounds and carrier with higher tumor cell accumulation without normal tissue accumulation are being searched. BSH don't have the active accumulation to tumor cells, but it has 12 x 10B in one molecule, BSH induces a strong biological effect even with small accumulation. Folate receptor-α (FR-α) is highly expressed on the many tumor (ovarian, kidney, colorectal, et al.), and it is useful as a target for drug delivery system (DDS) against cancer. It has been reported that the compound which is a cyclic oligosaccharide cyclodextrin modified with folic acid, has improved tumor accumulation and therapeutic effects of paclitaxel (PTX) and doxorubicin (DOX), which are anticancer drugs. In this study, we aimed to construct BSH inclusions with folate-modified cyclodextrin (ND 201) and to realize active accumulation of BSH against folate-targeted tumor and its usefulness.

[Materials and Methods] Colon-26 cells derived from murine colorectal cancer and A549 cells derived from human lung cancer were purchased from RIKEN BioResource Research Center. Colon-26 cells show the overexpression of FR and A549 cells show low expression level of FR. BALB/c nu/nu mice were used for in vivo kinetics experiments. BSH was purchased from Stella Pharma in powder form and dissolved in a phosphate buffer at the appropriate time before the experiment. ND201 was purchased from NanoDex corporation and dissolved in 0.1 mol/l carbonic acid/bicarbonate buffer (pH9-10). The solution was neutralized with a phosphate buffer (pH 6.8-7.2) and stocked at -30°C freezer. The interaction between BSH and ND201 was evaluated from stability constants and stoichiometric ratio. BSH and BSH containing ND201 (BSH-ND201) were administered from the tail vein to mice at concentrations of 100 and 5 mg/kg, respectively. Boron concentration (ppm) in the tumor and blood was measured with ICPS-8100 (Shimadzu Corporation) and the tumor/blood (T/B) ratio was calculated with each value.

[Results and Discussion] The stability constants Kc was 1.4×104 (/ M) in BSH and the value suggests that ND201 and BSH shows stable complex in serum-containing culture medium and human blood. The stoichiometry of a host-guest complex was determined by the continuous variation plot method. The plots made by monitoring the fluorescence intensity change gave a maximum peak at 0.5, indicating that ND201 forms an inclusion complex with BSH at a 1:1 molar ratio. Next, the boron concentration in tumors and blood of BALB/c nu/nu mice was measured by ICP-MS. The concentration in blood showed similar time course kinetics after BSH and BSH-ND201 without depending on the tumor type. On the other hand, the concentration in Colon-26 tumor showed drastic decrease immediately after BSH administration, whereas it increased to 24 hours and showed high value at 72 hours after BSH-ND201 administration. The T/B ratio when the intratumoral boron concentration was peak was calculated and BSH-ND201 showed high

T/B ratio (10.6) for Colon-26 tumor, and this value satisfied the T/B ratio > 10 required for clinical safety in BNCT. On the other hand, the ratio was too low (1.6) for A549 tumor.

[Conclusion] It was suggested that chemical modification targeting folate receptor to existing boron compounds may contribute to improvement of therapeutic effect of BNCT.

Keyword: BNCT, DDS, Folate receptor, cyclodextrin, BSH

PS1 R 02

The role of GM-CSF during early cellular responses after BNCR and gamma irradiation

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Introduction: Boron neutron capture therapy (BNCT) is one of the particle beam radiation therapy that causes alpha particle and lithium nuclei of high linear-energy-transfer in a short range. Boron neutron capture reaction (BNCR) can preferentially damage cancer cells using boron-carrier drugs that can be selectively distributed in cancer cells. Extensive DNA damage responses including those for DNA double strand breaks and apoptosis have been observed after BNCR.

Materials and Methods: We performed comprehensive analysis of mRNA expression and proteome using human squamous carcinoma SAS cells after BNCR in the KUR facility. To understand the biological significance of GM-CSF after photon beam and BNCR, we introduced CSF2 siRNA into cancer cells and effects on cell survival and responses were investigated.

Results: We found that the expression of CSF2 mRNA was increased 6 and 24 hrs after BNCR. Its gene product, granulocyte-macrophage colony stimulating factor (GM-CSF), was found to be augmented in the culture medium using ELISA. The siRNA of CSF2 induced reduction in CSF2 mRNA level to around 20% in a cancer cell line and GM-CSF level also decreased in the culture supernatant. The siRNA treatment of CSF2 limitedly affected the cell survival after gamma-ray irradiation.

Conclusion: It is implied that CSF2 may be involved in cancer cell survival after photon bean radiation and possibly after BNCR as an autocrine manner.

Keyword: BNCT, GM-CSF, CSF2, SAS cell

PS1 R 03

188Re-liposome, a high energy beta-particle radiopharmaceutical shows enhanced efficacy on suppression of head and neck squamous cell carcinoma progression by repeated doses

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Repeated administration of radiopharmaceuticals has been investigated in treating the advanced stage of human disease. In this study, we compared the effects of single dose and repeated doses of polyethylene glycol (PEG) decorated liposome encapsulated 188Re (188Re-liposome) on human head and neck squamous cell carcinoma (HNSCC) using the orthotopic tumor model. In addition, we further investigated whether the inhibitory effects of 188Re-liposome on HNSCC were associated with microRNAs. Human hypopharyngeal FaDu carcinoma cells expressing a luciferase reporter gene were used to establish the orthotopic tumor model via buccal injection. 188Re-liposome was manufactured by conjugating 188Re and N, N-bis(2-mercaptoethyl)-N9, N9-diethylethylenediamine (BMEDA) followed by embedding into the PEGylated liposome. Cerenkov luminescence imaging (CLI) was performed to assess the tumor accumulation of 188Re-liposome after single or repeated intravenous injection. The therapeutic efficacy was determined by measuring tumor growth rate, animal survival rate and tumor markers expression. The toxicity of 188Re-liposome was evaluated by body weight and blood counts of tumor-bearing mice after treatment. Accumulation of 188Re-liposome in various organs was determined by the biodistribution, and internal doses were calculated using the OLINDA/EXM software. The pharmacokinetics of 188Re-liposome was analyzed using the WinNolin software.

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The microRNA profiles were detected with microRNA open array. CLI revealed that accumulation of 188Re-liposome in tumors was increased by repeated doses compared to single dose. Repeated doses also enhanced the tumor suppression and elongated the survival of tumor-bearing mice. These effects were associated with Ki-67 proliferative marker and EMT related markers that were better inhibited in tumors treated with repeated doses. However, repeated doses of 188Re-liposome showed stronger effects on decline of blood counts than single dose, but not on the change of body weights. Furthermore, the circulation time of 188Re-liposome was longer using repeated doses. Biodistribution analysis revealed an increased accumulation of 188Re-liposome in bone marrow and tumor after repeated injection. The dosimetric estimation showed that the ratio of absorbed doses for 1g tumor treated with repeated doses and single dose was about 2. The effective doses of single dose and repeated dose of 188Re-liposome were 0.177mSv/MBq and 0.245mSv/MBq, respectively. miRNA array results showed that several tumor proliferation-related microRNAs changed after the treatment of 188Re-liposome. Among them, miRNA-182, a biomarker that has related to HNSCC, decreased obviously in 188Re-liposome treated tumors. Current data suggest that repeated therapy of 188Re-liposome provides enhanced internal circulation, tumor suppression and survival extension compared to single administration in the HNSCC tumor model. The results of this study would provide the fundamental molecular bioinformatics for prognosis of clinical applications and personalized medicine in the future.

Keyword: 188Re-liposome, HNSCC, beta-particle emitter, microRNA arra

PS1 R 04

The combination effect of neutron irradiation and exposure to DNA-alkylating agent on glioblastoma cell lines with different MGMT and p53 status

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Introduction / Temozolomide (TMZ) is a DNA-alkylating agent which is used for chemo-radiotherapy in the treatment of glioblastoma. This cancer is also one of the target cancers for Boron neutron capture therapy (BNCT). Although a function of O6-methylguanine DNA methyltransferase (MGMT) which is a DNA repair enzyme and p53 which is a tumour suppressor gene are sometimes mutated in glioblastoma cells, it is not known whether such a mutation affects cell sensitivity to neutron irradiation. In this paper, we discuss the sensitivity of the glioblastoma cell lines of T98G which is p53 mutated and high levels of MGMT activity and A172 which is p53 wild and low levels of MGMT activity after exposure to neutron irradiation and TMZ.

Materials and Methods / Glioma cell lines, T98G and A172 were obtained from RIKEN CELL BANK, Tsukuba, Japan. The exponential growing cells were exposed to TMZ for 24 h. After the removal of TMZ, the cells were transferred into a Teflon tube and irradiated with a thermal-neutron beam in the Research Reactor of Kyoto University. BNCT experiment was done with L-BPA (4-Borono-L-phenylalanine, Sigma-Aldrich). The irradiated cells were checked to determine the cell survival rate using the conventional colony formation assay immediately after the neutron irradiation.

Results and Conclusion / T98G cells were more resistant to TMZ treatment than A172 cells. The IC50 value for T98G was higher 10 times more than A172. TMZ treatment did at not change the cell killing effect of neutron irradiation in A172 cells with or without BPA. In constant, T98G cells showed more resistant to the neutron irradiation when BPA existed. These results possibility indicate that the activity of DNA repair of T98G cells might increase due to the expression status of MGMT after TMZ treatment. The difference in the MGMT and p53 status of the glioblastoma cells may be important factor to predict the effect of the combination therapy of BNCT and DNA-alkylating agent.

Keyword: Tenozolomide, MGMT, p53

PS1 R 05

Biological evaluation of boric acid uptake at different administration times. Comparative study between BPA and BA accumulation curves.

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Introduction: The biodistribution of boronophenylanaline (BPA) as a suitable compound for BNCT is well known. On the contrary, few data has been reported regarding boric acid (BA) biodistribution studies. Since 2013 our group was focused in biodistribution studies

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of boron in calcified tissues, administered as BA. Based on the high concentrations of B measured in calcified tissues (both in the ossification zone and the compact bone) when animals were infused with a solution of BA, we proposed the use of this compound as a potential carrier of boron to be delivered to osteosarcoma tumors. Under the hypothesis that the osteoblastic tumors behavior would be similar to endochondral ossification zone of the normal bone, we seek the understanding of the metabolism of boric acid (BA), with special interest in bone. In previous works, we performed a comparative biodistribution study between boric acid and boronophenylalanine, administered in the same doses (40 mg B/BW). In the present work we studied the boron uptake (both delivered as BPA and BA) of different tissues at several biodistribution's time intervals. The aim was to compare the accumulation curves of both compounds in calcified tissues, among others.

Materials and Methods: Wistar rats (120-140 g BW) were divided in two groups: the first group was injected with boric acid (BA, 200 mg B/kg BW). This BA concentration was chosen based on previous works done in our laboratory. The second group was infused with borophenilanaline (BPA, 40 mg B/kg BW). Both compounds were administered intraperitoneally (i.p.). The animals were sacrificed under anesthesia at different times after boron injection, from15 min to 6 h. Different tissues were excised and conserved at -20°C to be measured by ICP-OES. Bone marrow was extracted from diaphysis in order to obtain samples only containing compact tissue. Knee joint (endochondral ossification zone) was also excised. Liver, kidney, skin and blood were obtained to be used as reference tissues. All samples were digested, diluted and measured by ICP-OES.

Results: Great amounts of boron were registered in knee and diaphysis, with a maximum at 2 h after boron injection (about 300 ppm for animals injected with BA). At 6 h, a significant amount of boron was still present in calcified tissues corresponding to the BA protocol (75-100 ppm). The ratio bone/blood was also greater for BA in comparison with BPA for all the studied times. Differences in compound clearance were observed as well. According to the obtained results, a lapse of 2 h would be optimal between BA administration and irradiation, for a potential BNCT treatment considering that at that time the highest accumulation values of boron are observed in bone. However the highest bone/blood ratio was observed at 6 h post administration. It was also determined that the ratio bone/skin was 4 to 9 times greater than the one corresponding to BPA. This is a remarkable observation since the skin is a dose limiting tissue. Finally, microdistribution studies are being performed by autoradiography with nuclear track detectors.

Conclusion: The obtained results demonstrate a selective boron uptake in calcified tissues, mainly endochondral ossification zone (knee) when BA is administrated. This differential uptake could resemble the preferential accumulation of boron in tumor, as bone tumors behave in a similar manner as growing bone. These results are important for a therapeutic proposal, but also for the study of the radiotoxic effect in a BNCT potential treatment.

Keyword: boric acid, bone, osteosarcoma

PS1 R 06

Overexpression of LAT1 by lipofection enhances BPA intracellular incorporation in glioblastoma cells

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Boron neutron capture therapy (BNCT) is expected to be an attractive radiotherapy for invasive brain cancer. Outcome from BNCT largely depends on amount of intracellular accumulation of boron compound. L-type amino-acid transporter 1 (LAT1), through which boronophenylalanine (BPA) is transported into cells, is predominantly expressed in various types of tumor cells including glioblastoma but not in normal cells. We transfected pCMV/LAT1-GFP plasmids into a glioblastoma cell line, T98G, and selected several clones. Confocal laser microscopic observation confirmed that those clones overexpress LAT1 in cell membrane. Intracellular incorporation of 14C-BPA was measured by use of a RI tracer method in the LAT1-overexpressing T98G cells. The amount of intracellular incorporation of 14C-BPA was 1.5-5.0 times larger in LAT1-overexpressing clones than that in control clones. Cell growth rate was not affected by the LAT1 overexpression. We intend to examine the sensitivity to neutrons in LAT1-overexpressing T98G cells after BPA treatment using a linear accelerator.

Keyword: LAT1, BPA, glioblastoma, lipofection

PS1 R 07

Radiolabeling and In Vivo Image Evaluation of Boron containing neuropeptide (NPY) analogue in breast cancer

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Boron Neutron Capture Therapy (BNCT) is a cancer treatment method combined with target treatment with radiotherapy. It can selectively destroy cancer cells without serious damage to surrounding tissues. The boron-containing drug which can be high accumulated in cancer is a very necessary element for BNCT. We selected a truncated neuropeptide (NPY) analogue containing boron, as a target drug for breast cancer.
Neuropeptide Y (NPY) receptors are a family of G protein-coupled receptors and can be divided into five subtypes.In breast cancer, Y1R was over-expressed in tumors, The aims of this study were to evaluate 4T1 tumor image of boron-loaded NPY analog as a breast cancer probe.
We synthesized a Boron containing NPY analogue -DOTA-GSG-(2B)NPY4. It was chelated with 1, 4, 7, 10-tetraazacyclododecane-N, N′, N″, N‴-tetra acetic acid (DOTA) and contained with two m-Carborane-1, 7-dicarboxylic acids (C4H12B10O4). DOTA-GSG-(2B)NPY4 can be radiolabeled with isotope 111In or 177Lu in high temperature(80~100) about 5~15 minutes. Radio-TLC and Radio-HPLC are used for analyzing labeling efficiency. In animal study, tumor xenografts were performed in 6-wk-old female BALB/c mice by subcutaneous injection of 2 x 106 4T1 cells, and nanoSPECT/CT imaging was performed at 0.5 h, 2 h, 4 h, 24 h after injection.
The labeling efficiency of In111-DOTA-GSG-(2B)NPY4 is greater than 90%. In vivo study, the nano SPECT image of 4T1 animal model revealed that In111-DOTA-GSG-(2B) NPY4 has tumor uptake value (ID%/g>3)and tumor to muscle (T/M>2) ratio in 24 hours after tail vein injection.
The result shows the Radiolabeled boron containing neuropeptide(NPY) analogue In111-DOTA-GSG-(2B)NPY4 has high labeling efficiency(>90%). It also has high tumor uptake value and high tumor to muscle ratio. In111-DOTA-GSG-(2B)NPY4 can be a potential candidate drug in breast tumor for BNCT.

Keyword: neuropeptide(NPY), boron, breast cancer

Abstracts Posters

PS1 R 08

Disruption of Hif-1α enhances the sensitivity to BNCT in murine squamous cell carcinoma

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Introduction: The tumor microenvironment (e.g. hypoxia) has been suggested to play important roles in resistance to radiation therapy. Attempts to sensitize tumor cells by exploiting the tumor microenvironment have been studied. Hypoxia inducible factor 1 (HIF-1) is a major mediator of the cellular hypoxic response and a potential target for cancer therapy because it transcriptionally regulates a number of genes (including those involved in glucose metabolism, angiogenesis and resistance to chemotherapy and radiation therapy). In this study, we investigated whether the disruption of Hif-1α gene affects the radio-sensitivity of murine squamous cell carcinoma (SCC VII) cells to the boron neutron capture reaction (BNCR).

Materials and methods: The Heavy Water Facility of the Kyoto University Research Reactor (KUR) was used for neutron mixed beam irradiation. SCC VII and SCC VII-Hif-1α-deficient cell suspensions were incubated with 10B-carrier (BPA or BSH) at 20 ppm 2h before neutron irradiation, and cell survival assay was performed. After the subcutaneous injection of 10B-carrier in vivo, tumor-bearing mice were irradiated with a reactor neutron beam, and then clonogenic cell survival assay and micronucleus (MN) assay were performed. To examine the time course of the 10B concentration in solid tumors and blood, 10B-carrier solution was administered to the tumor-bearing mice subcutaneously into nuchal sites. The 10B concentrations in these tissues were measured by prompt gamma-ray spectrometry.

Results: SCC VII and SCC VII-Hif-1α-deficient cell suspensions were incubated with 10B-carrier (BPA or BSH), and then irradiated with the neutron mixed beam. The surviving fractions for cells incubated with BPA were lower than those with BSH in both SCC VII and SCC VII Hif-1α-deficient cells. We next investigated in vivo biodistribution of the 10B-carriers and found that the 10B biodistribution patterns in SCC VII Hif-1α-deficient tumors was similar to that in SCC VII tumors. Clonogenic cell survival assay after in vivo irradiation showed that SCC VII Hif-1α-deficient cells were more sensitive than SCC VII cells.

Conclusion: The disruption of Hif-1 gene does not affect the 10B concentration in solid tumors, but enhances the radiosensitivity of SCC VII tumor cells.

Keyword: BNCT, Hif-1α, 10B-carrier

PS1 Ch 01

Boron Tracedrugs: Drug-Design Challenge For Neutron Dynamic Therapy

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We developed boron tracedrugs for neutron dynamic therapy (NDT), based on our medicinal chemistry on targeted boron carrier drugs for boron nuclear capture therapy (BNCT) (Hori & Terada, 2016). Boron tracedrugs have on-demand medicinal characters being drugs when irradiated by neutron beams, to be combined therapeutics with diagnostics, thus, "theragnostics".
We present the overview of our concepts and some experimental results of boron tracedrugs as neutron dynamic therapeutics focusing protein degradations to apply to cancer and neurodegenerative diseases such as Alzheimer's disease including advanced glycation end products (AGEs). We also present the X-ray analysis of complex of a boron tracedrug, UTX-97 with lysozyme as the first molecular-level evidence of boron-drug-protein interactions (Morimoto & Hori et al., 2016). We expect our boron tracedrug could be promising new type of drugs in BNCT and recently emerging proton boron capture therapy (PBCT), as well as NDT, in the near future.

Keyword: Boron tracedrug, UTX-97, X-ray analysis, Neutron dynamic therapy, Alzheimer's disease

PS1 Ch 02

Difference in BPA uptake between glioma stem cells and their cancerous cells

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Introduction
Human glioblastoma multiforme (GBM) is the most aggressive type of brain tumor. Glioma stem cells are the cells most responsible for therapeutic resistance, and their presence is one of the main reasons for the poor prognosis of GBM. In a previous study, we reported on boron uptake in an in vitro GBM stem cell model, showing that it was significantly lower than that of typical glioma cells. Here, we report on the change in boron uptake related to stem cell carcinogenesis.

Materials and Methods
Cell lines
Tumor sphere-forming (TS) glioma stem cells model were obtained from Dr Osuka, Keio University, and were maintained in D-MEM/F-12 medium.
Boron agents
10B-enriched p-boronophenylalanine (BPA) was converted to a fructose complex by mixing a 1:1 molar ratio of BPA and fructose. The boron concentration was measured by means of inductively coupled plasma-atomic emission spectrometry (ICP-AES).
Brain tumor model
Five-week-old female C57BL/6J mice were used for the brain tumor model. TS cells (1 x 10e5) were inoculated into the right brain hemispheres of the mice. After 10 days, the tumor-bearing mice received BPA (250 mg/kg) intravenously via the tail vein. To examine boron uptake in tissues, the mice were sacrificed at 30 min or 1, 2, 3 or 6 h after drug administration, and samples of the blood, skin, muscle, liver, kidney, left brain hemisphere (normal brain), and right brain hemisphere (brain tumor) tissues were taken. The samples were wet-ashed with nitric acid.
Cancerous cells
Cancerous cells were obtained as follows. TS cells were inoculated subcutaneously into the right flanks of the mice. The mice were sacrificed 10 days after the injection. The subcutaneous tumors were cut with scissors into small pieces and were passed through a

mesh to make a single-cell suspension. The single cells were cultured for 5 days as cancerous cells. Then, 40 μg10B/mL BPA was added to each culture flask, and the cultures were incubated for 1, 3, 6, 12, and 24 hours at 37. Thereafter, the cells were harvested and the boron concentration was measured by means of ICP-AES and compared with that in TS cells cultured under the same boron administration conditions.

Results
In the brain tumor model experiment, the boron concentration in the tumor-bearing hemisphere at 1 hour after boron administration was 10.45 ± 0.78 μg/g, and in the normal brain hemisphere it was 7.01 ± 0.53 μg/g. The tumor tissue/normal brain boron concentration ratio was 1.48, showing a significant difference in boron accumulation.
In the experiment with cancerous cells, the boron concentration at 24 hours was 0.80 ± 0.09 μg/10e7 in the TS cells, whereas it was 1.08 ± 0.08 μg/10e7 in the cancerous cells, thus showing an increasing trend.

Discussion
In the experiment of the brain tumor model, we compared the brain tumor hemisphere with the normal brain hemisphere. Because it was technically impossible in the current experiment to extract only brain tumor tissue, we compared the concentration in the tumor-bearing hemisphere with that in the normal hemisphere. Thus, since brain tissue other than brain tumor tissue was included, the boron concentration might have been lower than its actual value.
BPA is a derivative of phenylalanine, which is an essential amino acid and thought to be taken up by cancer cells via L-type amino acid transporter 1 (LAT1). The possibility exists that LAT1 expression increases in glioma stem cells that become cancerous; such increase in LAT1 expression in glioma stem cells is an issue of our further experiments.

Keywords: glioma stem cells BPA

PS1 Ch 04

In vitro studies of new boron-rich nanostructures for BNCT

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Introduction
The development of new boron compounds for the goal of achieving greater tumor uptake than usual with those used in clinical trials is a very important research line in BNCT. Nanostructures are specially interesting because they could potentially carry a lot of boron atoms to tumor cells if they have an appropriate size for getting into the tumors by means of the enhanced permeation and retention effect. We have synthesized both at Granada and Grenoble new boron rich nanostructures and we have started the studies by irradiation with a cold neutron beam at ILL, Grenoble.

Materials and Methods
The cytotoxicity of the new boron nanostructures has been studied by observing the response in vitro to the addition of different quantities of these compounds. Melanoma cells (A375) and normal cell lines (MCR5) have been used. The cell uptake has been observed by means of flow cytometry and confocal imaging. The response of cells to irradiation with an intense thermal-equivalent cold neutron beam at the PF1b line at ILL has been measured by means of clonogenicity assays.

Results
It has been observed a greater killing effect of the irradiation on the tumor cells treated with some of the boron formulations. The compound biological effectiveness (CBE) has been estimated by direct observation of the cell survival after irradiation of the tumor cells. Results will be shown.

Conclusion
The promising killing effect of the irradiation for tumor cells treated with different boron-rich based nanoparticle encourages further researches with different cell lines and/or in vivo studies.

Keyword: boron compounds, nanoparticles, in vitro studies, clonogenic assays

PS1 Ch 05

Development of cyclic RGD-functionalized maleimide-containing closo-dodecaborate albumin conjugate (MID-AC) as an active tumor targeting boron carrier for neutron capture therapy

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Abstracts Posters

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<Introduction>
Boron neutron capture therapy (BNCT) functions as a double targeting therapy for cancer. Its therapeutic effect is realized by neutron beam irradiation and a boron delivery system. Although L-BPA is now in phase clinical study of brain tumor and head and neck cancer in accelerated-based BNCT, there is still an urgent need to develop new 10B carriers that deliver a sufficient concentration of 10B atoms to a tumor to realize effective BNCT for a wide variety of cancer treatments. We have focused on a serum albumin as a boron carrier. Serum albumin is a native protein and a major component of blood plasma. Serum albumin behaves as a compound carrier in blood, and the compound bound to serum albumin can circulate in blood without draining. Moreover serum albumin is accumulated in tumor tissue due to enhanced permeability and retention (EPR) effect. For example, Abraxane® is a human serum albumin-bound form of paclitaxel. Abraxane reduces the cytotoxicity of paclitaxel and compensates for the lack of water solubility of paclitaxel. We previously reported maleimide-containing closo-dodecaborate albumin conjugate (MID-AC). Maleimide-containing closo-dodecaborate (MID) was found to conjugate to free SH of cysteine and lysine residues in bovine serum albumin (BSA) under physiological conditions, forming highly boronated BSA that showed high and selective accumulation in tumor and significant tumor growth inhibition in colon 26 tumor-bearing mice subjected to thermal neutron irradiation. In this paper, we focused cyclic RGD peptide for tumor active targeting. Cyclic RGD is known to strongly bind to αvβ3 integrin which is overexpressing on many cancer cells and neovascularities. We designed the cyclic RGD-functionalized MID-AC as tumor active targeting boron carriers and evaluated their biological activity.

<Materials and Methods>
We synthesized MID by the nucleophilic ring-opening reaction of closo-dodecaborate-1, 4-dioxane complex with ammonia. In general, a maleimide group reacts with free SH of cysteine residues in protein under physiological conditions, MID has been found to react with both cysteine and lysine residues. Therefore, we first treated BSA with tetramethylrhodamine (TAMRA)-6-maleimide followed by MID (double modification method) to prepare TAMRA-MID-AC. We next prepared cyclic RGD-functionalized maleimide-containing closo-dodecaborate albumin conjugate (MID-AC) by the double modification method. BSA was first reacted with cyclic RGD-maleimide (cRGDfK-Mal) in PBS (pH7.4), subsequently reacted with MID. After ultrafiltration, the double-modified cRGD-MID-AC was obtained. The cell-uptake experiments of cRGD-MID-AC were carried out with U-87MG (human brain cancer, αvβ3 positive) and PC-3 (human prostate cancer, αvβ3 negative) cells and the boron accumulation in cells was determined by immunostaining using anti-MID antibody. Furthermore, we examined the in vivo biodistribution of cRGD-MID-AC and MID-AC using U-87MG xenograft model mice. cRGD-MID-AC or MID-AC were injected via the tail vein and the boron concentration in tumor tissue were determined by ICP-OES.

<Results>
cRGD-MID-AC was significantly accumulated into U-87MG cells. Interestingly, the accumulation of cRGD-MID-AC into PC-3 cells was lower than that into U-87MG cells, indicating that cRGD-MID-AC interacts with αvβ3 integrin and accumulate into αvβ3 positive cells, selectively. Furthermore, higher accumulation of cRGD-MID-AC in tumor was observed in the U-87MG xenograft model mice compared with MID-AC.

<Conclusion>
We succeeded in the preparation of cRGD-MID-AC using the double modification method. cRGD-MID-AC has a function of targeting αvβ3 positive tumors, thus it is considered to be a possible candidate as an active targeting boron carrier to tumor for BNCT.

Keyword: cyclic RGD peptide; active targeting; serum albumin; maleimide-containing closo-dodecaborate (MID)

PS1 Ch 06

Gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs) for neutron capture therapy of cancer: Influence of particle size of Gd-nanoCPs on tumor-killing effect in vitro

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Introduction: Gadolinium neutron-capture therapy (Gd-NCT) is cancer therapy that utilizes γ-rays and electrons emitted as a result of 157Gd (n, γ) 158Gd reactions. We have been developing gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs) as a means of controlling Gd delivery in Gd-NCT. Accumulation of Gd in Gd-nanoCP–treated tumors is based primarily on the bioadhesive (cationic), biocompatible (nontoxic), and biodegradable (bioerodible) properties of chitosan nanoparticles. Our previous studies demonstrated that neutron-capture reactions after intratumoral (i.t.) injection of Gd-nanoCPs in tumor-bearing mice can significantly suppress tumor growth; however, the inhomogeneous distribution of Gd-nanoCPs in tumor masses prevents complete cure. In addition, it is not clear how γ-rays and electrons relate to the tumor-killing effect. One can expect that reducing chitosan particle size in Gd-nanoCPs will improve the heterogeneous distribution of Gd in tumor tissues and increase the tumor-killing effect of electrons by shortening the adhesion length between Gd-nanoCPs and tumor cells. Thus, we aimed to investigate the effect of nanoparticle size on the tumor-killing effect of Gd-nanoCPs in Gd-NCT.

Materials and methods: Gd-nanoCPs were prepared with chitosan and Gd diethylenetriamine pentaacetic acid (Gd-DTPA) using a water-in-oil (w/o) emulsion-droplet coalescence technique. Two grades of chitosan with different molecular weights (MWs; 10 and 950 kDa) were used to manipulate Gd-nanoCP particle size. B16F10 mouse melanoma cells were employed to evaluate the cellular association properties of Gd-nanoCPs and the tumor-killing effect of thermal neutron irradiation. Tumor-killing effect was evaluated by a cellular viability assay after thermal neutron irradiation.

Results: The use of two grades of chitosan made it possible to obtain Gd-nanoCPs of different sizes and Gd content: Gd-nanoCPs prepared using chitosan with a higher MW (950 kDa) had a mean particle size and Gd content of 468 nm and 7.5 wt%, respectively (Gd-nanoCP-400); Gd-nanoCPs prepared using chitosan with a lower MW (10 kDa) had a mean particle size and Gd content of 185 nm and 24 wt%, respectively (Gd-nanoCP-200). The tumor-killing effect of Gd-nanoCPs in the Gd-NCT groups was significant, but efficacy was dependent on the micrometric properties of Gd-nanoCPs. Most notably, Gd-nanoCP-200 exhibited a stronger tumor-killing effect than did Gd-nanoCP-400 at the same Gd dose, and the tumor-killing effect of Gd-nanoCP-200 was the same as that of Gd-nanoCP-400 at less than half the Gd-nanoCP-400 Gd dose. This tumor-killing effect could be ascribed to the higher association between Gd-nanoCPs and tumor cells; improved distribution of Gd in cells exposed to Gd-nanoCP-200; and increased influences due to Auger and Coster-Kronig electrons, which have shorter path lengths and stronger tumor-killing ability than do γ-rays. Indeed, cells associated with uptake and adhesion that were exposed to Gd-nanoCP-200 had significantly higher Gd concentrations than those exposed to Gd-nanoCP-400 at the same Gd dose.

Conclusion: Our results demonstrated that reducing Gd-nanoCP particle size is an effective way to improve cellular affinity for Gd-nanoCPs and enhance the tumor-killing effect of Gd-NCT.

Keyword: Gadolinium, Nanoparticle, Chitosan

Thursday, November 1, 2018

Group I

PS2 CI 01

Preliminary study of the impact on dose distribution due to the reproducibility of shoulder position in sitting-positioned BNCT for head and neck cancer

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Introduction: In our institution, boron neutron capture therapy (BNCT) for head and neck cancer patient is often performed in a sitting position. Computed tomography (CT) image for treatment planning is acquired in a supine or prone position intended to reproduce the treatment posture as much as possible. However, how much the dose distribution is affected by the setup reproducibility between a sitting and a decubitus position has not been clarified, because it is difficult to ensure the setup reproducibility in a case of lower neck lesion. Therefore, we aimed to quantitatively evaluate the impact of reproducibility of ipsilateral shoulder position on dose distribution in sitting-positioned BNCT for the patient with lower neck lesion.

Materials and Methods: The CT image dataset of a recurrent head and neck cancer patient with a solitary right cervical lymph node metastasis was analyzed. Tumor, oral and pharyngeal mucosa and other normal tissue were delineated on the CT image, and the dose distribution was calculated with Simulation Environment for Radiotherapy Applications (SERA). The beam data of accelerator-based BNCT in our institution was used for dose calculation. The delineated shoulder position was changed gradually by rotating only ipsilateral shoulder at an interval 5° from -20° (opened shoulder) to +20° (closed shoulder)

on program. The dose distribution was calculated on each condition using the same beam parameters as the original plan. Blood boron concentration was assumed to be 25 ppm, and tissue-to-blood (T/B) ratios of boron concentration for tumor and mucosa were 3.5 and 1.0, respectively. The compound biological effectiveness (CBE) factors were 3.8 and 4.9, respectively. The dose was prescribed as the maximum dose of 15 Gy-Eq to mucosa. The impact of ipsilateral shoulder reproducibility was evaluated by dose-volume parameters for tumor and mucosa. The minimum dose (Dmin), maximum dose (Dmax), mean dose (Dmean), and dose delivered to 95% of target volume (D95) for tumor, and Dmean, D2cc, and D0.1cc for mucosa were evaluated using in-house software.

Results: For tumor dose, the Dmin and D95 in the closed shoulder plans tended to become lower than the original plan (max: -10.64% and -7.48%). The Dmean was decreased in the most plans compared with the original plan. The Dmax in the opened shoulder plans was decreased and in the closed plans was increased. On the other hand, for mucosa, the D2cc, D0.1cc and Dmax in the opened shoulder plans were higher than the original plan (max: +6.12%, +4.25% and +4.13%). The Dmean was increased depending on the ipsilateral shoulder position closed.

Conclusion: In BNCT for head and neck cancer, the impact on dose distribution for tumor and mucosa due to the ipsilateral shoulder reproducibility between a sitting and a decubitus position was evaluated. If the ipsilateral shoulder was reproduced with less than ±10° in the decubitus position, the dose errors of tumor and mucosa were approximately 5% in the selected case. Although further investigations of more cases are needed, it was confirmed that the dose distribution for tumor and mucosa was tended to affect by the ipsilateral shoulder reproducibility.

Keyword: BNCT, head and neck, treatment planning, DVH

PS2 Cl 02

Impact of inter-observer variability for mucosal delineation on the dosimetry of boron neutron capture therapy for head and neck cancer

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Introduction

In boron neutron capture therapy (BNCT) for the head and neck, prescribed dose for tumor is passively determined following the dose constraint for oral and pharyngeal mucosa that is recognized to be an organ at risk in BNCT. However, there is the potential failure risk that the different level of tumor dose may be prescribed by each institution and observer due to the inconsistent mucosal structure delineated even with the same mucosal constraint dose adopted. In this study, we aimed to elucidate the validity of T2-weighted magnetic resonance (MR) images which can depict the mucosa as a high intensity area to be used for delineating the mucosal structure.

Materials and Methods

Three patients with postoperative local recurrence including tongue cancer (patient 1), left parotid cancer (patient 2) and oropharyngeal cancer (patient 3) with less than 4 cm lesion, were enrolled in this study. Clinical image data sets for analysis contained computed tomography (CT) images and T2-weigheted MR images (T2WI). T2WIs were rigidly registered with CT images. By four radiation oncologists with more than 8 years career but no experience for BNCT, the first delineation of mucosa was performed based on the CT image data sets only (CT plan). Further 4 weeks after first delineation, the second delineation was performed based on the T2WI as well as the CT images (CT-MR plan). All treatment planning procedures were performed with a treatment planning system, SERA, and prescribed doses were defined as the mucosal maximum dose of 12 Gy-Eq. The values of tissue/blood ratio of the boron atom (T/B) and compound biological effectiveness (CBE) factor were assumed 1.0 and 4.9 for mucosa and 3.5 and 4.0 for tumor with a blood boron concentration of 25 ppm. All procedures except for delineation were performed by a medical physicist. The case-specific deviation based on inter-observer variability were evaluated for mucosal volume and target dose parameters, such as mean dose (Dmean), minimum dose (Dmin), and dose delivered to 95% of target volume (D95) for tumor, and compared between CT plan and CT-MR plan.

Results

The values of mucosa volume in patient 1, patient 2 and patient 3 were 72.8±47.2 cc, 57.5±43.1 cc and 55.3 ± 52.2 cc on CT plan, and 101.4 ± 19.4 cc, 85.8 ± 14.6 cc and 114.8 ± 6.6 cc on CT-MR plan. The values of D95 in patient 1, patient 2 and patient 3 were 20.9 ± 0.2 Gy-Eq, 43.3 ± 7.9 Gy-Eq and 16.7 ± 2.5 Gy-Eq on CT plan, and 21.3 ± 0.5 Gy-Eq, 42.0 ± 1.3 Gy-Eq and 15.3 ± 0.2 Gy-Eq on CT-MR plan. For all patients, standard deviations of mucosa volume and tumor D95 on CT-MR plan were significantly less than CT plan. The other target dose parameters showed the same tendency. The deviations of target dose parameters were different from each other depending on tumor localization.

Conclusion
The delineation based on only CT images generates large inter-observer variability in BNCT treatment planning. Therefore, MR T2WI which can depict the mucosal structure as a high intensity area must be combined with CT images for delineation procedure to decreases the variability of treatment parameters derived from inter-observer error.

Keyword: head and neck, treatment planning, inter-observer variability, delineation, MRI

PS2 CI 03

Study on application of BNCT to synovial sarcoma

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Introduction: Synovial sarcoma is a relatively rare soft tissue malignant tumor that develops in the extremities of young adults. Histologically, it displays epithelial differentiation and is classified mainly into biphasic or monophasic subtype. The former has both distinct epithelial and sarcomatous components and the latter only has a sarcomatous component. The epithelial tumor cells are arranged in glands, papillary structures, and cellular nests. On the other hand, spindle-shaped cells diffusely proliferate in the sarcomatous component. Although the basis of treatment of synovial sarcoma is wide surgical resection, a combination of surgery and chemotherapy may be used when resection of the tumor is difficult. Because the 5-year survival rate of synovial sarcoma is still poor at around 60%, development of a new treatment method is desired. In the present study, we reported a case of synovial sarcoma treated with boron neutron capture therapy (BNCT) and investigated the expression of L-type amino acid transporter 1 (LAT1), which plays a crucial role in the incorporation of boron compound (BPA) into tumor cells, in synovial sarcomas.

Materials and Methods: The case treated with BNCT was a 42-year-old woman who had synovial sarcoma involving the sciatic nerve in the left thigh. She declined surgery because of the probability of neural paralysis attributable to the surgical procedure. Then chemotherapy was administered for almost 28 months; however, the tumor mass gradually increased. Thereafter, she consulted our department for BNCT administration. To investigate the potential of BNCT therapy for synovial sarcomas, LAT1 expression was immunohistochemically examined, using five cases of synovial sarcoma (two of biphasic and three of monophasic subtype). The case treated with BNCT was included in the immunohistochemical study and was monophasic subtype.

Results: F-BPA-PET examination for the patient revealed inhomogeneous selective uptake of BPA (Tumor/Blood (T/B) ratio 3.5). BNCT at a dose of 500 mg/kg of BPA-fructose was administered before irradiation. The dose distribution ranged between 16 Gy-Eq and 60 Gy-Eq to the tumor and 12.2 Gy-Eq to the skin. During the 30-min irradiation, the concentration of boron in the blood was 26.6 ppm. Imaging studies one month after BNCT showed no further growth of the tumor mass and no severe side effects. Currently, the patient is under follow-up observation. Immunohistochemical analyses demonstrated mild or moderate LAT1 expression in the epithelial component of two biphasic tumors. On the contrary, sarcomatous components of all five tumors but one showed negative or mild expression. The tumor treated with BNCT was negative. One monophasic tumor with a high proliferative activity, however, demonstrated moderate expression.

Conclusion: Despite almost negative expression of LAT1, F-BPA-PET showed selective uptake of BPA in the case treated with BNCT. During the short-term follow-up, no further tumor growth was observed and local tumor regulation was attained. The stronger expression of LAT1 in other tumors, especially in the epithelial component, may suggest that BNCT is potentially effective for synovial sarcoma. Further study is warranted.

Keyword: synovial sarcoma, BNCT, L-type amino acid transporter 1 (LAT1), immunohistochemical study

PS2 CI 04

Treatment of Major Cervical Artery Invasion of Head and Neck Cancer with Boron Neutron Capture Therapy

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Introduction:
We have performed Boron Neutron Capture Therapy (BNCT) only for treating recurrent head and neck cancers (HNC) for which there were no other effective treatments remaining. Most of these instances are advanced cases that have already undergone radiation therapy. Moreover, almost without exception, these cases exhibit major arterial invasions. In some cases of advanced arterial invasion, BNCT can cause arterial rupture, resulting in excessive bleeding, and is therefore a life-threatening complication of HNC. This condition is called Carotid Blow-out Syndrome (CBS), referring specifically to the rupture of the carotid artery.
We should avoid causing arterial rupture both before and after BNCT. To this end, we carried out coil embolization of the carotid artery for such patients because ligature hemostasis is not effective for fragile irradiated arteries.

Materials and Methods:
We carried out coil embolization for two recurrent tongue cancer cases in which the tumor invaded the major cervical artery.
The first case was a 56-year-old man with recurrent tongue squamous cell carcinoma(SCC). After surgical therapy and concurrent chemoradiotherapy(CCRT) at a certain hospital, the tongue carcinoma was recurrent at the sublingual area. He was transferred to our hospital and intra-vascular intervention and BNCT were successfully performed, and consequently massive tumor lysis occurred. The external carotid artery and superior thyroid artery were exposed in the skin defect area, and pseudoaneurysms were found on the artery, which typically rupture within a few days. We planned coil embolization because ligature of the artery was not suitable, given that the artery was fragile from irradiation.
The second case was a 48-year old man who also had recurrent tongue SCC. After surgery, CCRT and adjuvant chemotherapy at a previous medical facility a massive tumor remained in the lingual area. He underwent additional several treatments at our hospital. Subsequently, excessive arterial bleeding occurred. We could not identify the source of the bleeding. Angiography was performed, and found that the lingual artery had ruptured. We decided that we could not ligate the artery because of the fragility and anatomical location of the lingual artery. We planned coil embolization of not only the external but also the internal carotid artery after a carotid balloon occlusion test.

Results:
We successfully completed hemostasis of irradiated artery by coil embolization without any severe sequelae.

Conclusion:
Several key issues related to planning BNCT for major arterial invasion cases are as follows.
1. The cervical major arteries are fragile and have reduced self-regenerative power after conventional radiation therapy.
2. Tumor reduction after BNCT might cause rupture of a major artery, such as CBS, in certain advanced cases.
3. Coil embolization is an effective method to control major arterial rupture in some cases.

Keyword: CBS, interventional radiology, coil embolization, head and neck cancer, advanced cases

PS2 M 01

CURRENT STATUS OF NEUTRON CAPTURE THERAPY IN COLOMBIA

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Introduction
In Colombia during the year of 2013, a Medical Physics Master Program started activities at the Pontificia Universidad Javeriana (PUJ). In addition to the academic activities, the

master´s program also considered it convenient to conduct research. Taken into account the infrastructure and the experience of existing scientific staff at the University some research groups were established, in particular, a team is working on basic research for cancer treatment using Neutron Capture Therapy (NCT).

Materials and methods
The research project consists of four phases: pre-feasibility, feasibility, development and testing. The pre-feasibility and feasibility will provide the necessary information and the elements for the implementation of the project such as human resources, costs, times, infrastructure, among others. In the development phase it is projected the construction and commissioning of a neutron source with its respective moderator and in the final phase, irradiation tests with epithermal neutrons on a phantom will be carried out.
As a first action and in order to establish the relevance of the research, it was carried out a study of the state of the art using bibliographical resources. As a complementary action it was inquired in the country the available resources which could be used for the research. After that, it was proposed for the Medical Physics Master program an advanced course named Neutronic Radiation, which has been offered since 2015. At the same, it was registered a research project entitled Neutron Capture in Cancer Treatments (NCCT) at the Departamento Administrativo de Ciencia, Tecnología e Innovación (COLCIENCIAS).

Results
As results of all actions achieved during the last three years, the team has been able to establish preliminary collaboration agreements with the Lawrence Berkeley National Lab (LBNL), at the University of California, Berkeley in USA and the Servicio Geológico Colombiano (SGC) in Colombia. On the other hand, the team has elaborated a draft of a Proposal for Research Contract to be submitted to International Atomic Energy Agency (IAEA).
Since, for the Master of Medical Physics Master Program at the PUJ, the Neutronic Radiation course has been taught regularly for the last three years, several Master's thesis related to the main topics of the research project, have been finished and some others are currently being done. In order to establish a solid scientific community, the group established a collaboration with a team of the Universidad Distrital Francisco Jose de Caldas, in Colombia, and currently two undergraduate thesis are in progress. On the other hand, members of the research group have presented lectures, published articles and the last year participated in the Latin-American Symposium on Nuclear Physics and Applications (LASNPA) in Cuba.

Abstracts Posters

Conclusion
In Colombia during the last three years, an initiative for the treatment of cancer using NCT have begun. A research team at the PUJ leads most of all activities related to this initiative. Among the main achievements made up to date, it can be mentioned the preliminary collaboration agreements with national and international institutions, fill out a Proposal for Research Contract in order to submit it to IAEA and different tasks related to research in NCT which have been achieved in the Medical Physics Master Program.

Keyword: Keywords: Medical Physics, Master Program, research project, proposal for research contract.

PS2 M 02

Treatment Result of Combined Volumetric-Modulated Arc Therapy (VMAT) and Simultaneously Integrated Inner-escalated Boost (SIEB) Radiotherapy in a Patient with Locally Advanced Maxillary Sinus Carcinoma.

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Introduction:
Squamous cell carcinoma of the head and neck (SCCHN) occurs annually in >550, 000 people worldwide. Definitive concurrent chemoradiotherapy (CCRT) is a definitive treatment for the unresectable locally advanced head and neck cancer. However, it is relatively radioresistant in bulky tumor due to hypoxia relating to the poor blood supplying in the center of tumor. Also, Wada et al. found that hypoxia with <10% O2 reduced uptake of 10B-BPA because of decreased mRNA expression of LAT1, and may cause less effective in boron neutron capture therapy (BNCT).
Integrated Inner-escalated Boost (VMAT-SIEB) is a developed technique to overcome the radioresistant area in tumor with dose escalation in the center of gross tumor. Herein, we reported a promising outcome of locally advanced maxillary sinus cancer treating with CCRT combined VMAT-SIEB technique.

Materials and Methods:
Results: case reports Tracing the history, a 46-year-old man had diagnosed as having squamous cell carcinoma of left nasal cavity to left maxillary sinus, cT4a (anterior orbital content invasion; 3.2cm)N2bM0, stage IVA (2015/11, AJCC 7e).
On CT images, enhanced masses are found in left nasal cavity and left maxillary sinus with destruction of anterior and medial wall of left maxillary sinus, and obstructive left frontal, left ethmoid, left maxillary and sphenoid sinusitis. The largest mass measures 32.3mm in diameter. Multiple enlarged lymph (up to 10mm in short axis) nodes over the left level II and left level III neck were found. Definitive CCRT was planned due to his refusal of operation.
Thus, VMAT-SIEB radiotherapy was given. From the peripheral to the central zones of the gross maxillary sinus tumor, dose gradient of 300-350 cGy per fraction with initial 5 fraction, and then shifted to 250-300 cGy per fraction (at the previous 300-350 cGy per fraction isodose line) with further 20 fractions were prescribed. The conventional dose fractions of 200 cGy with 25 fractions were prescribed to the left frontal sinus, left ethmoid sinus, left maxillary sinus, sphenoid sinus, and high risk lymph nodes region. Hence, by 25 fractions, total dose of VMAT-SIEB with 6500-7750 cGy and conventional 5000 cGy were delivered to the gross maxillary sinus tumor and clinical risk area, respectively.
During and after radiotherapy, no severe toxicities were noted (grade 3-4). At about one year after completion of CCRT, regressed tumor with pathological CR status was noted. No recurrence and no new late RT toxicity had been noted since then.

Conclusion:
Definitive CCRT combined VMAT-SIEB techniques is useful for managing locally advanced maxillary sinus cancers, with a cost of limited toxicities. For improving response rate of BNCT of bulky tumor, radiotherapy combined VMAT-SIEB technique can be a additional modality of BNCT. Further prospective trials were encouraged to test the clinical effective size of this combined technique.

Keyword: simultaneously integrated inner-escalated boost, locally advanced maxillary sinus carcinoma

Abstracts Posters

PS2 M 03

Pilot study of Gadolinium Accumulation in Tumour with Intra-arterial Administration of Gadoteridol-Entrapped Water-in-Oil-in-Water Emulsion in VX-2 Rabbit Hepatic Cancer Model for Neutron Capture Therapy

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Abstracts Posters

[[Introduction] Gadolinium neutron capture therapy (GdNCT) is one of the non-invasive therapy approaches utilizing the auger electron and gamma ray produced after the reaction between gadolinium atoms and thermal neutrons. We had previously reported that Gadoteridol-entrapped anionic liposome and Gd-DTPA entrapped in Calcium Phosphate modified nanomicelle had revealed sufficient amount of gadolinium delivery and showed tumour growth suppression with thermal neutron irradiation. As the carrier of neutron capture agents for hepatocellular carcinoma, we also continue the study of application of WOW emulsion. In this study, we evaluated the data of VX-2 rabbit hepatic cancer model after intra-arterial injection of Gadoteridol entrapped WOW emulsion using ICP-AES, Laser ablation ICP-MS for gadolinium delivery, and histopathlogy for the evaluation of anti-tumour effect with GdNCT.

[Material & Methods] Gadoteridol solution (1396.5 mg/5ml) was filtrated by controlled pore glass membrane emulsifying into 5 ml of IPSO (Lipiodol) containing surfactant, and then formed the water-in-oil emulsion (WO). The WO emulsion was then emulsified again with aqueous phase containing 5 ml of saline and surfactant. With this double emulsifying technique, the Gadoteridol-entrapped WOW emulsion was prepared. The particle size distributions of the vesicles of WOW and IPSO microdroplets were determined with a laser-diffraction particle-size analyzer SALD-2000 (Shimadzu Corp., Kyoto, Japan). The size of WOW was controlled to 50 μm. WOW emulsions (Gadoteridol 93 mg/kg) were administrated with intra-arterial injections via proper hepatic artery compared with Gadoteridol-Lipiodol mix emulsion on VX-2 (Shope-virus derived Squamous Cell Carcinoma cell line) rabbit hepatic tumour models. One and three days after arterial injections, the gadolinium concentrations of the tumour nodules, normal liver tissues, and blood were measured. The gadolinium concentrations of tissues were determined by ICP-AES of Juntendo University. We also performed Laser ablation ICP-MS method for detection of the local distribution of gadolinium in the VX-2 tumour tissue and normal liver tissues after intra-arterial injection. Histopathological examination also performed to evaluate the therapeutic effects of GdNCT.

[Results and Discussion] Measurement of gadolinium concentration of tumour, normal liver and blood after intra-arterial injection of Gd-entrapped WOW emulsion or Gd/ISPO mix conventional emulsion in VX-2 hepatic cancer bearing rabbit model was performed. The concentration of Gadolinium after 24 hour of Gd-entrapped WOW emulsion intra-arterial injection in tumour, normal liver tissue, and blood were 329.04 ± 31.69 ppm, 199.24 ± 22.66 ppm, and 0.094 ± 0.002 ppm, respectively. In the case of Gd/ISPO mix conventional emulsion, the concentration were 1.796 ± 0.917 ppm, 0.644 ± 0.18 ppm, 0.008 ± 0.000 ppm, respectively. We firstly obtained the imaging of gadolinium atoms in the VX-2 tumours and normal liver tissues by Laser ablation ICP-MS. The accumulation of gadolinium atoms was seen at the boundary site of tumour in the group of Gd-entrapped WOW emulsion, but there was no detection in the group of Gd/ISPO mix conventional emulsion. The anti-tumour effect was observed after thermal neutron irradiation. Hyalinization and bleeding necrosis were seen in the pheripheral Grisons sheath of the tumour border regions. Disseminations into the peritoneum are not seen in the group of GdNCT.

[Conclusion] We prepared Gadoteridol-entrapped WOW emulsion for intra-arterial infusion to VX-2 hepatic tumour model. The Gadoteridol concentration in tumour by WOW emulsion was observed to be superior to those by conventional emulsion. We also firstly showed the imaging of Gadolinium atoms accumulation using Laser ablation ICP-MS. We recognized the anti-tumour effect with thermal neutron irradiation after intra-arterial injection Gadoteridol-entrapped WOW emulsion. We are ongoing to planning the in vivo evaluation of novel boron compound or gadolinium compound entrapped WOW emulsion with NCT.

Keyword: Hepatocellular carcinoma, WOW emulsion, intra-arterial injection, Gadolinium neutron capture

PS2 P 01

Neutron field characterization for Neutron Capture Therapies

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In the frame of a AB-BNCT project in the Laboratoire de Physique Subatomique et de Cosmologie (LPSC) in Grenoble, see D. Santos et al. presentation, we are developing original Berylium and Lithium targets and moderators adapted to deliver optimal ephithermal neutron profiles.

This project benefit of a neutron directional detector called MIMAC-FastN, developed by the LPSC-MIMAC team and well adapted to characterize the fast neutron field produced at the target level. The low energy nuclear reaction for neutron production currently studied is the 9Be(d (1.45 MeV), n)10B . The design of a rotating Berylium target and the thermal testing electron beam facility developed at the LPSC to perform the thermal vali-

dation will be shown. Different studies have been made on the optimization of a design of a Beam Shape Assembly and the penetrability of neutrons in brain using ICRU models.
The ability to characterize the fluence and the angular distribution of the neutron field produced will impact the design of the neutron moderator. This fast neutron directional detector and spectrometer MIMAC-Fastn will be also presented. Measurements of the fast neutron production performed recently by the detector will be described. Moreover, the results of the Monte Carlo MCNP simulations will be presented.

Keyword: beam shape assembly, neutron filed, characterization

PS2 P 02

Monte Carlo simulation-based design for an electron-linac-based neutron source for boron neutron capture therapy

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Accelerator-based BNCT requires high power accelerators and high heat dissipation targets. Photo-neutrons can be created by electrons as they strike targets of various materials at energies above the photo-neutron threshold which lies in the range of 6-MeV to 13-MeV for most materials. A large-sized target, a surface of which is irradiated by pulsed-electron beams that are scanned by magnetic field variation, can drop a heat density deposited by the pulsed-electron beams. Moreover, such a target will have an advantage of a long lifetime, since the dispersed electron beams on the target will hardly damage target materials. Therefore a beam shaping assembly with a large-sized target, a 60 × 60 cm surface of which is irradiated by pulsed-beams of 20-MeV electrons from a linac, was designed by Monte Carlo simulations.
In the design of an electron-linac-based target, the material and thickness of two targets were examined, in two physical processes: one is a photon producing target by (e, γ) bremsstrahlung reactions and the other is a neutron producing target that produces photo-neutrons by (γ, n) reactions. Further, the sizes of a Pb filter for reducing γ-rays in the radiation from the target and an MgF2 moderator for neutron filtration and a neutron beam collimator were determined so that the neutron beam fulfilled specific conditions which met the recommended beam-characteristics shown in IAEA-TECDOC-1223. It was assumed that a linac produces one hundred pulses per second of electron beam and a

part of the surface of the target is irradiated by the pulsed-electron beams in a manner of raster scan. With the irradiated area of a target as a parameter, beam characteristics at a treatment position including the epithermal neutron flux were calculated.
Calculation results showed that the photon producing target of a 0.3-cm-thick tungsten plate maximized the yield of (e, γ) bremsstrahlung. Examinations for the material and thickness of the neutron producing target are proceeding. Further, calculation results suggested that the irradiated area of a target effects beam characteristics at a treatment position.

Keyword: Electron linac, Pulsed-electron beam, Target, Bremsstrahlung, Neutron source

PS2 P 03

Measurement of gamma-ray dose and neutron activation in BNCT beams using TLD-200

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BNCT beams are mixed neutron and gamma-ray field where epithermal neutrons predominate the radiation dose. Due to the relatively low reproducibility of the TL reading and the relatively large thermal neutron sensitivity TLD-700 (7LiF:Mg, Ti) was reported to be not suitable for accurate in-phantom BNCT dosimetry. CaF2 TLDs in comparison with TLD-700 have very low thermal neutron sensitivity and therefore have obvious advantage for gamma-ray dose measurement in BNCT beams. When irradiated in BNCT beams the activators Dy in TLD-200 (CaF2:Dy) and Mn in TLD-400 (CaF2:Mn) became non-negligibly radioactive owing to their significant capture cross sections, 2700 barn for Dy and 13.3 barn for Mn. As a consequence, the CaF2 TLD will receive additional internal beta and gamma-ray irradiation through the decay of the radioactive activators, which results in the so-called self-irradiation dose. In this work TLD-200 chips were used to measure the gamma-ray doses free in air and in a 21 x 21 x 21 cm3 PMMA phantom exposed to the BNCT beam at Tsing Hua Open-pool Reactor (THOR). An optimum an-

nealing and readout process has been established where a 170°C 3 min pre-irradiation annealing and a 80°C 3 min post-irradiation annealing on a hot plate were chosen and the TL signal was read out at a heating rate of 10°C/s to 300°C and lasting for 10 s. The glow curve of TLD-200 shows a relatively clear and sharp peak at temperature around 180°C. The fading experiment showed that the TL signal decreases ~2% at the first day after irradiation with a half-life of ~33 days. At about three hours after irradiation either free in air or in the phantom TL signals of the TLD-200 chips were read out. The correction of the self-irradiation component induced by the decay of Dy-165 was achieved by applying a second readout of the TLD chip at about one day after irradiation. While the neutron dose contamination was estimated from the effective neutron dose which was obtained by multiplying the neutron spectra acquired from a Monte Carlo calculation for the experimental setup with the neutron effective dose conversion factor of TLD-200. With respective to the neutron activation caused by the BNCT beam it was analyzed by using the modified absolute calibration method to determine the Dy contend in the TLD-200 chip.

Keyword: TLD-200(CaF2:Dy), gamma-ray dose, effective neutron dose

PS2 P 04

Evaluation of neutron measurement system utilizing a LiCAF scintillator - optical fiber detector

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[Introduction]
In boron neutron capture threpy (BNCT), metal foil radio-activation method is primarily used for measuring neutron flux. However, since this method is complex and time consuming, methods utilizing a scintillator detector have been actively researched to achieve simple and real time measurements. Here, we report on an evaluation of neutron measurement system consisting of a LiCAF scintillator, optical fiber, photomultiplier tube, and readout electronics using the accelerator-based BNCT system.

[Materials and Methods]
In order to evaluate the accuracy of newly developed neutron measurement system, we measured neutron flux in a 20x20x20 cm water phantom and compared with that determined by the gold activation method. As a neutron source, we used a 30 MeV cyclotron-based epithermal neutron source (C-BENS) system manufactured by Sumitomo Heavy Industries, Ltd. that was installed at the Osaka Medical College Kansai BNCT medical center. We measured the neutron flux with depth along the beam axis as well as the in-field flux distribution for the collimator diameter of 12 cm.

[Results]
The in-phantom neutron flux distribution obtained by above new system was equivalent to that obtained by the gold activation method. Additionally, it took significantly less time to collect a flux distribution using the real-time system compared with the gold activation method.

[Conclusion]
We confirmed that the neutron flux obtained by the developed neutron measurement system was sufficiently accurate. Since simple and real-time measurements is possible by this system, we expect that the time necessary for periodic beam quality checks will be significantly reduced in a near future.

Keyword: neutron measurement system, LiCAF scintillator, optical fiber, gold activation method

PS2 P 05

Installation of accelerator-based BNCT system at Kansai BNCT Medical Center

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[Introduction]
Neutron sources for boron neutron capture therapy (BNCT) are in a transition phase from nuclear reactors to accelerators. A 30 MeV cyclotron-based epithermal neutron source (C-BENS) system manufactured by Sumitomo Heavy Industries, Ltd. was installed at Osaka Medical College, Kansai BNCT Medical Center. Additionally, a cyclotron for Radio Isotope production for PET was installed to carry out 18F-BPA PET for predicting BPA accumulation in tumors. Here, we report an overview of the facility and measurement results of neutron flux distribution in a water phantom.

[Material and Methods]
The building of the Osaka Medical College, Kansai BNCT Medical Center is 4 story architecture 3 above and 1 floor below the ground. C-BENS was installed on the first floor in 2017. C-BENS consist of 1 mA, 30 MeV proton cyclotron, beam transport system, neutron generation target, moderator, and collimator system. The size of proton beam from the cyclotron is expanded in the beam transport system to reduce the heat load on the target and incident of the beryllium target. Since high energy neutron is generated from the beryllium target, it is necessary to reduce the neutron energy from 28 MeV to epithermal neutron energy suitable for BNCT. The neutron beam was shaped by a collimator for irradiation. A horizontal beam port is installed in the irradiation room. The treatment bed moves to the irradiation room on the rail after setting the patient in the supine position or the sitting position in the preparation room. The treatment bed returns to the preparation room after irradiation by remote control in order to reduce the unnecessary radiation exposure to medical staff. The 2nd floor has the rooms for the patient's setting simulation and CT for treatment planning and a PET-CT was set up. In addition, a 20 MeV proton cyclotron for Radio Isotope production was installed on the first floor. It is possible to conduct 18F-BPA PET inspection. On the third floor there is a staff room and a lecture room for various purposes. The confirmation of proton current output and thermal neutron flux distribution on center axis in a water phantom were carried out as part of the acceptance test of C-BENS. A gold wire and a gold wire covered with the cadmium were placed along the beam central axis and irradiated with epithermal neutron beam. The radioactivity of the irradiated gold wire was measured using a high purity germanium semiconductor detector. The thermal neutron flux distribution was evaluated after deriving the reaction rate of activated gold wire.

[Results]
It was confirmed that the beam current from the 30 MeV proton cyclotron was 1 mA. The thermal neutron flux at the depth of 20 mm in the water phantom exceeded 10^9 (n / cm^2 / s) under the condition of the collimator diameter of 12 cm.

[Conclusion]
We introduced the overview of Osaka Medical College, Kansai BNCT Medical Center. In the installed C-BENS system, it was confirmed that the output of the proton beam current from the cyclotron and the thermal neutron flux intensity in a water phantom satisfied the desired value.

Keyword: cyclotron-based, epithermal neutron source, neutron flux, gold activation method

Group II

PS2 P 06

Rotary Type Beam profile monitor for Accelerator-Driven BNCT System

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(Introduction)
Recently, many types of the accelerator-based BNCT system have been developed in the world. In the system, low energy (2-30MeV) and high current (1-10mA) proton beam should be stably positioned in the beam line and securely irradiated on the target (Li and Be) for stable neutron production. To controle the beam precisely, it is very important to measure the beam position and profile by the in-situ measurement, but it is very difficult because the beam power is too high (>MW/m2) for a commercially available profile monitor. In Nagoya University, we are developing an accelerator-based neutron source for BNCT in conbination of a sealed lithium target and a DC accelerator (2.8MeV, 15mA). To monitor the low energy and high current proton beam, we are developing a rotary type beam profile monitor.

(Material & Method)
The rotary type profile monitor is constructed with a tungsten wire and it's rolling mechanism. The diameter and length of the tungsten wire are 2mm and 10cm, respectively and it is connected to the pulse motor shaft with a rod (length: 41mm) in parallel with the motor shaft. When the pulse motor is rotated through 180 degree, the wire will scanned (82mm) over the cross section of the proton beam (40mm in dia.). To keep the temperatue of the tungsten wire less than 800K, the swing speed of the wire is determined to 204rpm. In this condition, the effect of the thermionic electron emission can be neglect under the condition of every 30 sec measurement.

(Results)
We had set the rotary type profile monitor in the accelerator-based neutron system in the university and measured the position and profile of the proton beam before the neutron production experiment.

Keyword: wire scan profile monitor

Abstracts Posters

PS2 P 07

Design of Neutron Moderation Assembly for A-BNCT

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INTRODUCTION : An Accelerator-based Boron Neutron Capture Therapy (A-BNCT) system is now under development in South Korea. A-BNCT system is more compact and safer comparing to the system based on nuclear reactors, so that it can be installed in-hospital. It consists of a linear accelerator providing 10 MeV, 8 mA proton beams, and a neutron generation and moderation assembly to produce neutrons with an effective epithermal energy range for patient treatments. In the present study, we focus on design of the neutron moderation assembly which consists of fast neutron filter, main neutron moderator, thermal neutron filter, and neutron beam collimator.

METHODS AND MATERIALS : The 80 kW proton beam striking against a 45°-tilted thick Be target generates intense fast neutrons. Since epithermal neutrons are more effective for the cancer treatment of human body in BNCT, we need to moderate fast neutrons to epithermal neutrons of 0.4 eV ~ 40 keV energy range. In our design, W and Fe were used as the fast neutron filter, and AlF3 was chosen as a material of the main moderator, because AlF3 showed better performance than other well-known candidate materials such as MgF2, CaF2, and so on. LiF is used for thermal neutron filter. The moderator assembly is surrounded by lead (Pb) for reflecting neutrons and shielding gamma-rays, and borated polyethylene (BPE) for shielding neutrons. For the shaping of neutron beam profile for patient treatment, a step-tapered square collimator module is designed.

RESULTS : Neutron energy and flux distribution at the patient position were calculated with MCNPX 2.7.0 code and the design parameters were optimized by controlling materials, shapes, dimensions, and arrangements of moderator materials. We used isostatic powder compacted materials for AlF3 and LiF, instead of crystalline state. According to the results of MCNPX calculation, the proposed design satisfied all design criteria recommended by IAEA: epithermal neutron flux > 1.0x109/cm2/sec, epi-thermal to thermal neutron flux ratio > 20, and others such as fast-to-epithermal neutron flux ratio.

CONCLUSION : We designed a neutron moderator assembly for a BNCT facility in Korea. The design performances satisfied well the design criteria guided by IAEA. A poster will be presented with more details in this conference. ACKNOWLEDGEMENTS :This R&D was supported by the grant funded by MOTIE (Ministry of Trade, Industry and Energy) Grant No. 10063465.

Keyword: A-BNCT, neutron moderation assembly, AlF3

PS2 P 08

Results of the measurements of the 33S(n,α)30Si cross-section at CERN and ILL: application to NCT

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Introduction
The 33S(n, α)30Si was proposed as a cooperative reaction for tumours growing to the skin. Three experiments for determining the 33S(n, α)30Si cross-section in a wide energy range were proposed and accepted at CERN and ILL. The results of such experiments will be shown. Applications to NCT are discussed.

Material and Methods
The CERN experiments were performed at two different flight paths of the n_TOF facility. The ILL experiment was carried out at the PF1b experimental area.

Results
The experiments clarified the disagreements in the strongest resonance located at 13.45 keV and in the thermal value. Also the theoretical 1/v is confirmed. The doses delivered to tumours have been studied with these data.

Conclusion
The 33S(n, α)30Si could be of interest in NCT for certain tumour.

Keyword: Experiment, S33 as target, dose calculations

Abstracts Posters

PS2 P 09

ADVANCES OF THE CHARACTERIZATION OF NEUTRON CAPTURE BY BORON AND GADOLINIUM USING GEANT4

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Introduction

In Colombia, at the Pontificia Universidad Javeriana (PUJ), since the establishment of the research group on treatment of cancer using Neutron Capture Therapy (NCT) in 2015, our group has been focused exclusively on carrying out calculations with GEANT4 mainly because of its characteristics of open-source software (it can be modified or supplemented as needed by the end user) and its ample worldwide use and validation in the particle physics, space, and medical physics communities among others. Although there exist other Monte Carlo codes (i.e., MCNP) well established for the calculations we are performing, we have not resorted to them due to their user restrictions like accessibility and licensing. We consider the use of GEANT4 to study NCT processes can be proved to be very useful for comparison and development purposes with the other existing codes.
In this work, we study the central processes in Boron and Gadolinium neutron capture, in particular, the understanding and characterization of such processes using GEANT4.

Materials and methods

Nowadays, one of the most promising and potential therapies for cancer treatment consists of the combination of two elements: (1) a suitable beam of epithermal neutrons and (2) a drug marked with either Boron (10-B) or Gadolinium (157-Gd) which is to be stored in the cell. The neutron capture by Boron is referred to as BNCT while by Gadolinium, as GdNCT.
In BNCT, the main reaction (94% branching ratio) produces Lithium ions, alpha particles, and gamma rays [10 B + n -> 7 Li (0.84MeV) + 4 He (1.47MeV) + γ (0.48MeV)]. For the case of GdNCT, gamma rays, x rays, and internal conversion (IC) and Auger electrons are released after the corresponding neutron capture.
We study the above processes through a simulation in GEANT4. In order to do so, a beam of neutrons with energy of the order of few eV (0.2 eV for BNCT) is defined and a thin 10-B and 157-Gd foil are used as a target. Besides the standard physics packages, we are using the G4HadronPhysicsFTFP_BERT_HP library.

Results

For the case of BNCT, we have simulated samples of 106 events out of which about 11 % corresponds to neutrons interacting inelastically with B10. From these, we have reproduced the expected branching ratios:
• 93.8 %: 10 B + n -> 7 Li (~0.84MeV) + 4 He (~1.47MeV) + γ (~0.48MeV)
• 6.2 %: 10 B + n -> 7 Li (~1.01MeV) + 4 He (~1.78MeV)
For the case of GdNCT, although the energies of the outgoing gammas are correct, we have not been able yet to obtain the Auger and IC electrons expected in the neutron capture. The problem seems to be related to an improper simulation of the expected decay spectrum for 158-Gd due to lack of a complete list of the corresponding nuclear energy levels in GEANT4.

Conclusion

Our preliminary results indicate that the studies carried out in this work are feasible with GEANT4, however, we have encountered some difficulties to perform the characterization of both processes primarily due to the availability of the complete energetic neutron spectra for all involved processes which are still under implementation and development, and an apparent incomplete model for the nuclear structure of gadolinium. Work in order to solve these issues is ongoing. This will allow us to carry out a complete characterization for the Boron and Gadolinium neutron capture processes using GEANT4.

Keyword: NNeutron Capture, Boron, Gadolinium, characterization, Geant4

PS2 P 10

Accelerator based BNCT system in Nagoya University -Development of a sealed lithium target-

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An accelerator based neutron source for BNCT is currently under development with a combination of a DC accelerator and a compact sealed-lithium target in Nagoya University. To seal the lithium metal in the target, a titanium foil is used for covering the thin plate of the lithium metal settled on a tantalum base plate. A proton beam of 2.8 MeV and

Abstracts Posters

15 mA (42 kW) ejected from the accelerator will irradiate the lithium through the titanium foil (Irradiation area: 80 x 80mm2). To remove the high heal load from the target, we had developed a new cooling system with a strong turbulent flow in the water channels induced by the V-shaped staggered rib structure. In the previous study, a heat removing experiment was performed by utilizing electron beam of 40 kV in the Active Cooling Test Stand 2 (ACT2) at National Institute for Fusion Science (NIFS) for a cupper plate with the new cooling system (Cooling block of the lithium target). In the experiment, we had confirm the new cooling system could remove the high heat load of 42 kW, efficiently. Based on the result of the heat removable test, we had estimated the surface temperature of the target is about 180 degree C, when the heat load of the proton beam is 6.6 MW/m2. In the estimation, we assumed a good heat transfer rate between the titanium foil, the lithium metal and the target base plate, based on a mockup test about the wettability between those metals.

For confirming the good heat transfer rate in the sealed-lithium target, it is needed to irradiate the proton beam on the lithium target, but the lithium will produce the radioactive 7Be due to the 7Li(p, n)7Be reaction. To reduce the risk of the radiation exposure from the used lithium target, we used indium metal instead of lithium for the first step of heat removal test, because the liquid indium has similar specifications to the liquid lithium metal. To keep the good wettability, indium metal was melted by heaters in a vacuum chamber and funneled into the narrow space between the tantalum base plate and the titanium foil in the chamber. When the indium target was irradiated by proton beam from the accelerator, the surface of the target was measured by a radiation thermometer. We are evaluating the performance of the heat removal and the endurance of the titanium foil.

Keyword: accelerator based neutron source, sealed-lithium target, cooling system

PS2 P 11

Physical Design of Modular Neutron Source Device for AB-BNCT

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A modular BNCT neutron source device based on a small proton accelerator was designed and the physical design and parameter calculations were completed. The results are in good agreement with the IAEA recommended values. The design is based on an accelerator with a proton beam intensity of 1 mA and an energy of 14 MeV. The metal beryllium is used as the target material. The neutron shaping section uses aluminum fluoride, calcium fluoride and other slow-down materials, and adopts a modular design. The length of the neutron moderated section can be adjusted and the material can be replaced. The neutron spectrum needs to be different according to treatment conditions. Can give different solutions. The neutron beam parameters of the different designs of the neutron source device of the modular design are better than or close to the IAEA's recommended values. According to the physical design plan, the next detailed design and processing.

Keyword: BNCT neutron source, AB-BNCT, modular, neutron shaping device

PS2 P 12

High-accuracy measurement of the epithermal neutron flux of a 7Li(p,n)7Be-based BNCT neutron source with activation monitors

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Introduction: Boron neutron capture therapy (BNCT) is a very promising targeted cancer radiotherapy. The neutron source is a key factor for BNCT. The epithermal neutron (0.5 eV ~ 10 keV) flux is one of basic characteristics for recent BNCT neutron sources. The measurement accuracy of epithermal neutron flux of a BNCT neutron source directly relates to the trustworthiness of the treatment planning system. It matters not only to the target tumor dose but also to the protection of normal tissues and critical organs of treated patients. Providing a safer treatment environment for treated patients is no doubt a duty and it is also one of the keys to make BNCT comparable to conventional radiotherapies. Therefore, it is of great interest to accurately measure the epithermal neutron fluxes of BNCT neutron sources.

Materials and Methods: In the previous work, based on the activation using 71Ga(n, γ)-72Ga reaction, an epithermal neutron flux monitor and two neutron flux monitors from 20 keV to 1 MeV with GaN wafers as activation material have been developed using Monte Carlo simulations for BNCT. In this work, the previously developed activation monitors are employed to measure the epithermal neutron flux of a 7Li(p, n)7Be-based BNCT neu-

Abstracts Posters

tron source produced by an accelerator-based neutron source (ABNS) facility named cell selective particle therapy (CSePT), which is now being developed in Osaka University, Japan. MCNP5 is used to carry out the calculations.

Results: The epithermal neutron flux of the 7Li(p, n)7Be-based BNCT neutron source produced by CSePT can be measured to an accuracy of ~ 3.4% by the activation monitors.

Conclusion: It is concluded from the Monte Carlo simulation results that the epithermal neutron flux of the 7Li(p, n)7Be-based BNCT neutron source produced by CSePT can be measured to high accuracy by the activation monitors. The activation monitors will be efficiently applicable to evaluate the radiation doses and qualities of BNCT neutron sources.

Keyword: Epithermal neutron flux, Activation monitor, 7Li(p, n)7Be-based BNCT neutron source, CSePT

PS2 P 13

Neutron Photon irradiation damage analysis of human tissue for BNCT based on Geant4

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BNCT(Boron Neutron Capture Therapy) is an effective method for cancer treatment. The neutron and photon irradiation damage analysis of human tissues is of great significance for the solution design and effect evaluation of BNCT. The international general program development package (Geant4) is used in this paper to establish a three-dimensional numerical model of human tissue which is recommended by ICRP and the absorption of drugs with boron in the cancerous tissue of brain is considered in the model. The neutron and photon coupling transport model is constructed to analyze the energy deposition in the cancerous tissue from the neutron photon beam of one cyclotron and further estimate the radiation damage of the cancerous tissue and normal tissues by the factors such as the neutron beam intensity, the incidence direction, the action time and the concentration of boron containing drugs, which provides the theoretical evidence for the BNCT.

Keyword: BNCT, Geant4, neutron irradiation damage, drugs with boron

PS2 P 16

The Physical Design of a Modular Neutron Source Assembly for BNCT

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The physical design of a modular neutron source assembly for BNCT based on a compact cyclotron was completed and the major characteristic parameters of the output neutron beam from the assembly meet the recommended values proposed by IAEA. The assembly comprises of a beryllium target bombarded by a 1mA proton current with energy of 14MeV, a neutron moderating section, a spectrum shifting section, a beam collimating section and several shielding layers. Aluminum fluoride and calcium fluoride are used as slowing-down materials. In order to satisfy different requirements for neutron energy range in therapy, the neutron spectrum of the output beam could be adjusted by changing the structure and composition of the spectrum shifting section. Now the assembly is undergoing detailed mechanical design and then fabrication will be carried out. Next year a series of experiments will be carried out on it.

Keyword: BNCT, modular neutron source assembly, neutron spectrum

PS2 P 18

BEAM DOSIMETRY EQUIPMENT FOR THE NUBEAM BNCT SUITE AT HELSINKI UNIVERSITY HOSPITAL CANCER CENTER

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Helsinki University Hospital (HUH) and Neutron Therapeutics (NT) have a joint project to install a nuBeam neutron source for boron-neutron capture therapy (BNCT) in the HUH Cancer Center. HUH Cancer Center is setting up a beam dosimetry system for characterization of the neutron beam and subsequent dose quality management.
When establishing the system and methods 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)) are followed.
In this presentation the equipment and methods are described:
1. Activation detector sets for
   a. Neutron spectrum determination
   b. Neutron fluence measurement for
      i. Free beam geometry measurements
      ii. Neutron field distribution in phantoms
      iii. Neutron dose recording in patient irradiations
2. Gamma spectrometer system for measurement of the activation detectors
3. Paired ionization chamber system (Mg(Ar) and TE(TE)) for the measurements of the total, fast neutron, and photon absorbed dose.
4. Water filled reference phantom for
   a. Mapping the neutron fluence using activation detectors
   b. Mapping the dose distribution using the paired ionization system
5. Solid material phantoms for regular and periodic quality control measurements
6. Anthropomorphic phantoms for verification measurements of the treatment planning system (TPS)
7. Beam monitoring system

Keyword: Beam monitoring system

Group III

PS2 R 01

Biodistribution of Boric Acid (BA) and Boronphenyalanine (BPA) for BNCT in the hamster cheek pouch oral cancer model

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Introduction: We previously proved the therapeutic potential of the chemically non-selective boron compound decahydrodecaborate (GB-10) as a stand-alone boron carrier for BNCT in the hamster cheek pouch oral cancer model. Although GB-10 was not taken up selectively by oral tumor tissue, it contributed to homogenous boron targeting of all tumor cell populations, an asset when treating heterogeneous tumors. In the case of GB-10-BNCT, selective tumor lethality would result from selective damage to aberrant tumor blood vessels. Furthermore, BNCT efficacy was enhanced when GB-10 and boronophenylalanine (BPA) were administered jointly. We previously performed biodistribution studies with Boric Acid (BA) alone in the hamster cheek pouch oral cancer model. Based on the working hypothesis that BA and GB-10 will behave similarly in tissues, the aim of the present study was to perform biodistribution studies of BA + BPA administered jointly in the hamster cheek pouch oral cancer model as a starting point to contribute to the knowledge of (BA+BPA)-BNCT radiobiology for head and neck cancer and optimize therapeutic efficacy.

Materials and methods: The right cheek pouch of Syrian hamsters was subjected to topical administration of the carcinogen dimethyl-benzanthracene twice a week for 12 weeks. Once the exophytic tumors, i.e. squamous cell carcinomas, had developed, the animals were used for biodistribution studies with BA + BPA. Four administration protocols with different proportions of each of the compounds were assessed: 1. BA, 50 mg 10B/kg, iv + BPA, 15.5 mg 10B/kg, iv; 2. BA, 34.5 mg 10B/kg, iv + BPA, 31 mg 10B/kg, iv; 3. BA, 20 mg 10B/kg, iv + BPA, 46.5 mg 10B/kg, iv; BA, 10 mg 10B/kg, iv + BPA, 55.5 mg 10B/kg, iv. For all 4 protocols the total boron dose administered was within the same range (65.5 - 66.5 mg 10B/kg). BA was administered one hour before BPA. Groups of animals were euthanized 4 h after the administration of BA and 3 h after the administration of BPA. Samples of blood, tumor, precancerous tissue, normal pouch tissue, liver, spleen and kidney were processed for ICP-OES boron measurements. In addition, samples were excised and sectioned using a novel procedure to include the tumor with the insertion zone and the surrounding precancerous tissue in a single section (TIP section) to study boron microdistribution using the neutron autoradiography technique. Results: Considering the clinically most relevant tissues in the case of head and neck cancer, mean boron concentration fell within the same range of widespread values for all 4 protocols in the case of tumor (73-83 ppm), precancerous tissue (49-57 ppm) and normal pouch tissue (43-60 ppm). Liver, kidney and spleen values were similar for all 4 protocols, with mean values ranging from 28 to 55 ppm, 45-80 ppm and 32-50, respectively. Preferential tumor uptake vs precancerous tissue (T/Pr) and normal pouch tissue (T/NT) was observed for all 4 protocols, with ratios ranging from 1.2 to 1.8. While the boron value in the tumor was similar for the 4 protocols, differences in blood boron concentration were observed, decreasing from 64 to 24 ppm as the proportion of BA fell. Tumor/blood ratios were in the range of 1.1 to 3.6.

Conclusion: The BA + BPA administration protocols at a similar total boron dose, delivered similar, therapeutically potentially useful boron content to tumor with a large spread in values. The degree of selectivity in tumor uptake improved by increasing the proportion of BPA. Ongoing neutron autoradiography studies seek to determine 10B microdistribution in tissue. Dosimetric calculations indicate that the absolute boron values reported would be in a therapeutically useful range for in vivo BNCT studies at the RA-3 Nuclear Reactor.

Keyword: Biodistribution, Boric Acid, BPA, oral cancer model, BNCT

PS2 R 02

OPTIMIZATION OF THE CLASSICAL CHEMICAL CANCERIZATION PROTOCOL IN THE HAMSTER CHEEK POUCH TO STUDY BNCT FOR ORAL CANCER

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Introduction Head and neck squamous cell carcinoma (HNSCC) is an epithelial cancer, arising from the mucosa of the upper aerodigestive tract. The most frequent tumor sites of HNSCC are the larynx, the pharynx, and the oral cavity. Various animal models have been developed for studying pathogenesis, genetic background and novel therapeutic development in HNSCC. The hamster buccal pouch carcinogenesis model recapitulates oral oncogenesis, and research in this model is focused on carcinogenesis and cancer treatment. Our group proposed and validated the hamster cheek pouch model of oral cancer for boron neutron capture therapy (BNCT) studies. It is based on the topical application of subthreshold doses of the complete carcinogen, 7, 12-dimethylbenz[a]anthracene (DMBA). However, this protocol has an important limitation: DMBA chemical cancerization induces initial severe mucositis, affecting animal´s welfare and causing tissue loss and pouch shortening. “Short” pouches cannot be everted for local irradiation for BNCT. Our aim was to optimize the DMBA classical cancerization protocol to avoid initial severe mucositis, without affecting tumor development, and perform BNCT studies in animals cancerized with this novel protocol. This optimization of the classical cancerization protocol would improve animal´s welfare and reduce the number of animals needed for our BNCT studies, contributing to the 3R´s (particularly refinement and reduction) ethical principles for the care and use of laboratory animals. Materials and Methods We studied <Group 1> Classical cancerization protocol, no interruptions (24 applications) and <Group 2> Classical with two interruptions (the 2 skipped topical applications are completed at the end of the cancerization protocol, i.e. a total of 24 applications). We studied mucositis, length of the pouch and tumor development during cancerization and two months after the end of the cancerization protocol. Also histological studies were performed in each group one month after the end of cancerization. Two groups cancerized with either the classical or the interrupted protocol were treated with BNCT mediated by the boron compound boronophenylalanine (BPA, 15.5 mg 10B/kg). Irradiations were performed at the RA-3 nuclear reactor. Total absorbed dose was prescribed to precancerous tissue (10 ppm boron concentration) and was in the range 2.0 Gy - 2.6 Gy. Results Group 1 (classical cancerization protocol) exhibited a significantly higher percentage of animals with initial severe mucositis and “short” pouches versus Group 2 (interrupted cancerization protocol) (71% vs 17% and 50% vs 0%, respectively). Tumor development was not affected by the interruptions. Histological studies confirmed similar characteristics for both groups. Overall tumor response induced by BNCT was 76% in both groups with a similar incidence of BNCT related severe mucositis for Groups 1 vs 2 (86% vs 71%, respectively). Conclusion The twice-interrupted protocol reduced severe mucositis during cancerization, favouring the animal’s welfare and reducing the number of cancerized animals needed for our studies (Refinement and Reduction principles). The optimized protocol did not affect tumor development, the histological characteristics of tumor and precancerous tissue, or BNCT induced tumor response and associated radiotoxicity.

Keyword: Oral cancer, Mucositis, Hamster cheek pouch, BNCT, replacement and reduction and refinement

PS2 R 03

NOVEL ORAL CANCER & PRECANCER EXPERIMENTAL MODEL FOR SIMULTANEOUS LONG TERM EVALUATION OF THE EFFECT OF BNCT ON TUMORS AND PRECANCEROUS TISSUE

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Introduction Unresectable head and neck tumors are treated with radiation therapy or chemoradiotherapy, but the dose that can be administered to tumor is limited by toxicity in precancerous tissue. Oral mucositis is a frequent, dose-limiting side effect which represents an important unmet medical need in oncology practice. Besides, the development of new tumors (second primary tumors) in the precancerous tissue surrounding tumor adversely influences patient prognosis. We previously evidenced BNCT therapeutic efficacy to treat tumors in an oral cancer model induced by a 12-week cancerization protocol, but this model was aggressive in terms of tumor development and carcinogen toxicity, and yielded an overly radiosensitive precancerous tissue. We then developed a precancer model (6-week cancerization protocol) which gave rise to a precancerous tissue that mimicked more closely human field cancerized tissue. However, primary tumors were not present at the time of irradiation, precluding a tumor control study coupled to the study of precancerous tissue. The aim of the present study was to characterize an oral cancer & precancer model in the hamster cheek pouch induced by an 8-week cancerization protocol, proposed previously by our group. For the first time, in this model, we performed boron biodistribution studies and assessed whether BNCT is capable of treating tumor and the surrounding precancerous tissue simultaneously, without exceeding the radiotolerance of precancerous tissue. Materials and Methods Hamsters cancerized with the 8-week protocol (DMBA application, twice a week during 8 weeks) were selected to perform biodistribution studies using BPA (boronophenylalanine) and exposed to BPA-BNCT: CONTROL: cancerized no BNCT; BNCT 4 Gy absorbed dose to precancerous tissue; BNCT 3 Gy; BNCT 2 Gy. Tumor development and histologic features were evaluated in the Control group. We evaluated the therapeutic effect of BNCT on tumors present at the time of irradiation (T0), and on the development of new tumors from precancerous tissue and associated radiotoxicity. Outcome was evaluated one month post BNCT. Results Three months post-cancerization protocol, >60% of the animals exhibited tumors and were amenable to treatment. The animals were followed during 6 months after the end of the cancerization protocol. Histologic features of tumor and precancerous tissue confirmed that the 8-week cancerization model was less aggressive than the 12-week cancerization model but more aggressive than the 6-week cancerization model. Tumor, precancerous tissue and blood boron uptake were: 20.7+/-5.6 ppm (n=7), 13.4 ppm (n=2), 6.9 ppm (n=2) respectively.

The 4Gy BNCT group induced severe mucositis in precancerous tissue in 83% of the animals, and virtually none of the tumors were amenable to evaluation due to severe mucositis in precancerous tissue leading to tissue necrosis. Instead, in both BNCT 3Gy and 2Gy groups, we were able to evaluate tumor control. In these preliminary studies, BNCT exerted a therapeutic effect on tumors that were present at the time of irradiation. BNCT 3Gy induced a higher % of animals with severe mucositis and a higher % of animals with new tumors versus BNCT 2Gy (50% vs 17% and 50% vs 33% respectively). Conclusion The oral cancer & precancer model induced by an 8-week cancerization protocol allows for the simultaneous study of the effect of BNCT on tumors and on tumor development and mucositis in precancerous tissue. The dose prescribed to the dose-limiting precancerous tissue must be carefully chosen, as mucositis as a side effect could promote tumor development in precancerous tissue. Future studies will be focused on increasing the sample size of the BNCT 3Gy and 2Gy groups. We will also study radioprotectors that would allow us to increase the dose prescribed to the dose-limiting precancerous tissue and improve BNCT tumor control and its inhibitory effect on tumor development.

Keyword: Oral cancer & precancer model, BPA, biodistribution study, BNCT, mucositis

PS2 R 04

RADIOTOXICITY INDUCED BY BNCT MEDIATED BY BPA: A COMPARATIVE ANALYSIS IN AN ORAL CANCER MODEL EMPLOYING THREE DIFFERENT CANCERIZATION PROTOCOLS

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Introduction Every oral cancer patient involves a unique set of challenging, complex and multidisciplinary clinical issues. Most of the cases are largely due to both individual

Abstracts Posters

predisposition (specific genetic characteristics) and exposure to carcinogens, caused by lifestyle. In patients with frequent contact with cancerous agents, the concept of field-cancerization is related to a greater risk of developing one or more carcinomas. Therefore, the study of different oral cancer patient scenarios is of particular interest. In some cases, oral tumours can be removed surgically. However, incomplete removal of tumor tissue or tumors not amenable to surgery require radiotherapy. Radiation is individually determined for each patient and requires long-term follow up, because surveillance for new tumors and recurrent cancers in field-cancerized tissue is important. Oral mucositis in field-cancerized tissue, an adverse effect of many cancer therapies, is a frequent, unresolved challenge and dose-limiting side effect that impacts on patient survival and quality of life. Therefore, there is a need for more effective and selective therapies and studies in appropriate experimental models are pivotal to progress in this field. The hamster cheek pouch is a widely known animal model to study oral mucositis and that closely mimics events involved in the development of premalignant and malignant human oral lesions. It is based on the topical application of subthreshold doses of the complete carcinogen, 7, 12-dimethylbenz[a]anthracene (DMBA). Unlike models of implanted tumor cells in normal tissue, this model mimics the spontaneous process of malignant transformation. It also provides a tumor model surrounded by precancerous tissue which gives rise to the formation of additional tumors, as occurs in precancerous human oral mucosa. The hamster cheek pouch model of oral cancer was proposed and validated by our group to study BNCT. We performed BNCT employing three different cancerization protocols, intending to mimic three different "clinical" scenarios: (1) The classical protocol to study the effect of BNCT on tumors and the short term effect on an overly radiosensitive and aggressive precancerous tissue in terms of tumor development (24 DMBA applications; Tumor model); (2) The less aggressive protocol to study the long term inhibitory effect of BNCT on the development of new tumors and mucositis in precancerous tissue (12 DMBA applications; Precancer model); (3) The newly studied 8-week cancerization protocol (16 DMBA applications) that allowed the study of the therapeutic efficacy of BNCT on tumors, the inhibitory effect of BNCT on the development of new tumors in precancerous tissue and associated mucositis in precancerous tissue simultaneously (Tumor & Precancer model). In the present analysis, we compared BNCT mediated by BPA induced radiotoxicity, evaluated as oral mucositis in precancerous tissue, for each cancerization protocol. The classical carcinogenesis protocol was used for studies at the RA-3 and RA-6 nuclear reactors in Argentina. As mucositis is a still unresolved challenge, we assessed the radioprotective effect of Histamine for each protocol. Results Radiotoxicity increases with the aggressiveness of the carcinogenesis protocol that in turn increases with the number of applications of DMBA (carcinogen), e.g. at 2 Gy absorbed dose (RA-3 nuclear reactor) 80% of the animals exhibited severe mucositis in the 24-applications protocol (Tumor model), 17% in the 16-applications protocol (Tumor & Precancer model) and 0% in the 12-applications protocol (Precancer model). Histamine reduced severe mucositis in precancerous tissue induced by the 12-applications protocol but, to date, did not exert a radioprotective effect in the 24 and 16-applications protocols. Conclusion In this animal experimental model, we demonstrated that BNCT-induced mucositis increases with the aggressiveness of the carcinogenesis protocol employed. This finding should be taken into account when populations who are at a high or low oral cancer risk are considered for BNCT.

Keyword: Oral cancer & precancer models, BNCT-BPA, Mucositis, "Clinical" scenarios

PS2 R 07

Investigation of the biological properties of neutron beam of accelerator-based BNCT system with intestinal crypt regeneration and ICP-AES

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[Introduction] Boron neutron capture therapy (BNCT) is based on nuclear reaction between thermal neutron and boron-10. The reaction causes alpha particle and lithium nuclei in a short range with high energy. For that reaction, it is necessary that boron compound such as 10B-boronophenylalanine (BPA) should be preferably introduced into cancer cells. Neutron beam irradiation is also essential process for BNCT. Recently, accelerator-based BNCT system has been developed and installed in several facilities. The biological properties of neutron beam in each BNCT system should be evaluated to improve and optimize the therapy. We have started to evaluate the biological effectiveness of the neutron beam and BNCT system in NCC.

[Materials and Methods]
Intestinal crypt regeneration has been used to evaluate the relative biological effectiveness of particle beam radiations including proton and carbon beams. Previously, BALB/c mouse strain has been used for the measurement. In this study, we have used C57BL/6J male mice for the measurement of intestinal crypt regeneration to evaluate and compare biological properties of gamma-ray, neutron beam and BNCT. C57BL/6J male mice were given BPA by intraperitoneal administration. Mice were irradiated with neutron beam with accelerator-based BNCT system CICS-1 or irradiated with gamma-ray. Before irradiation, BPA was i.p administrated and whole body irradiation was carried out. Irradiated thermal neutron was detected by radioacitivation of small gold wire and gamma-ray dose was measured using by glass dosimeter. Three mice were also set in stratified positions to evaluate the biological effect of neutron beam in the depth direction. Approximately 4 days after irradiation, the treated mice were sacrificed and the jejunum was collected and cut into pieces, and crypt numbers were counted. The diluted blood and jejunum were pre-treated with hydrogen peroxide and perchloric acid to measure boron concentration with ICP-AES.

[Results and Conclusions]
Numbers of crypt decreased dose-dependently after gamma-irradiation and after BNCT condition. Intestinal crypt regeneration may be useful for evaluation of biological effect of BNCT.

Keyword: ICP-AES, Boron concentration, Crypt

PS2 R 08

Influence of oxygen status on therapeutic effect of boron neutron capture therapy in human tumor cells

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Abstracts Posters

Introduction: Antitumor effect of boron neutron capture therapy (BNCT) depends on double strand breaks of DNA attacked by heavy charge particles generated by 10B(n, α)7Li reaction. Therefore, the uptake of 10B agent in tumor cells is a key factor that considerably influences a therapeutic effect. Although it is known that the uptake of 10B-boronophenylalanine (BPA) into tumor cells is suppressed by under hypoxic condition that occurs frequently in tumor tissue and it is a significant event that leads deterioration in a therapeutic effect, few studies have focused on that. Therefore, we investigated the influence of hypoxic condition on therapeutic effect in BNCT and effectiveness of reoxygenation and hyperbaric oxygen.

Materials and methods: T98G human glioblastoma cells, HepG2 human liver hepatocellular cells, TE-5 human esophageal squamous cancer cells, and MCF-7 human breast cancer cells were incubated under normoxia or hypoxia (1% O2) for 24 h, followed by 2-h incubation under sustained oxygen condition or carbogen (95% O2/ 5% CO2). For L-type amino acid transporter 1 (LAT1) expression, first-strand cDNA was synthesized from extracted total RNA and gene expression of LAT1 was assessed by real-time reverse transcription polymerase chain reaction (RT-PCR). For evaluation of intracellular boron concentration, the cells were incubated with BPA at 30 μg 10B/ml for 2 h following 24-h incubation. After that, 10B concentration was analyzed by inductively coupled plasma atomic emission spectroscopy (ICP-AES). For cell survival after neutron irradiation, treated cells with BPA were exposed to an accelerator-based neutron beam with the irradiation charge amount of 0.2 C. Following irradiation, clonogenic assays were carried out.

Results: The mRNA expression of LAT1 under hypoxia was significantly decreased in all cell lines in comparison with normoxia. The BPA uptake under hypoxia was also decreased compared to normoxia as well. Furthermore, the survival rate of hypoxic cells after neutron irradiation was higher than that of normoxia. Incubation with carbogen following hypoxia slightly increased LAT1 mRNA expression in cells. The BPA uptake of these cells was increased compared with cells incubated under sustained hypoxia, and there was a significant difference in T98G cells.

Conclusion: The reduction of the BPA uptake caused by hypoxia was partially reversible. It is possible that the effect of reoxygenation for hypoxic cells and the degree of improvement of BPA uptake ability under carbogen differ in the type of cancer cells. Reoxygenation may help improve the therapeutic effect for hypoxic cells in BNCT with BPA.

Keyword: boronophenylalanine, L-type amino acid transporter 1, hypoxia, reoxygenation

Abstracts Posters

PS2 Ch 01

Boron-rich oil-in-water emulsions as drug nanocarriers for boron neutron capture therapy

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Introduction: Boron Neutron Capture Therapy (BNCT) is a binary approach to cancer therapy which relies in the accumulation of boron-rich drugs in the tumour, followed by irradiation with thermal neutrons to trigger a nuclear reaction that creates selective damage in the tumour tissue. Recently, nanomaterials have been proposed as promising drug carriers capable to accumulate high boron load in the tumor tissue thanks to the well known enhanced permeability and retention (EPR) effect. In this work, we propose the preparation, radiolabelling and preliminary in vivo evaluation of cobalt bis(dicarbollide)-stabilized, o-carborane-loaded oil-in-water (o/w) nanoemulsions as potential boron-rich BNCT drug candidates.

Methods: To prepare the nanoemulsions, a dissolution containing o-carborane in a triglyceride oil based on docosahexanoic acid was prepared and poured into a second solution containing cobalt bis(dicarbollide) in pure water, and the mixture was sonicated under vigorous stirring in a cold bath. Hydrodynamic diameter and colloidal stability were investigated using dynamic light scattering. For imaging experiments, the solution containing o-carborane was spiked with 1-[18F]fluorocarborane, prepared using a previously reported method. The biodistribution of the labelled nanoemulsions after intravenous administration in rats was followed up to 6 hours post-administration using positron-emission tomography (PET) imaging.

Results: Stable nanoemulsions with average hydrodynamic diameter around 160 nm and ζ-pot of -72 mVs could be efficiently prepared. The nanoemulsion proved to be stable up to 4 months after preparation at room temperature. Distribution studies performed in rats after intravenous administration showed significant accumulation in the liver at short times after administration, and the activity progressively translocated to the gastrointestinal track at later time points. Blood samples confirmed that around 0.1% of the radioactivity remained in blood at 3 hours after administration, suggesting that circulation time should be sufficient to enable accumulation in the tumour in future experiments. The lack of radioactivity in bones suggests negligible defluorination of the labelled carborane.
Conclusions: Boron-rich, stable nanoemulsions could be prepared using a simple and robust methodology. In vivo biodistribution studies in rats suggest potential application of the novel nanosystems as BNCT drugs. Studies in different xenograft mouse tumour models to assess the capability of the novel nanosystems to accumulate boron atoms in the tumour are currently being conducted.

Keywords: BNCT, emulsion, nanocarrier, EPR

PS2 Ch 02

Functional evaluation of kojic acid-modified carborane developed as a boron drug for melanoma BNCT

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[Introduction]
Highly metastatic melanoma (melanoma) is one of the serious targets of boron neutron capture therapy (BNCT). BNCT drugs require high boron occupancy, cancer cell specificity and high water solubility. In this study, using kojic acid conjugate, kojic acid-modified carborane (CKA), which is suggested to have boron cluster o-carborane and have affinity for melanocyte. Hydroxypropyl-β-cyclodextrin (HP-β-CD) was used to include CKA in order to increase the water solubility. This highly water-soluble complex (CKA/HP-β-CD) was evaluated as a novel boron agent for melanoma BNCT. After evaluating the function of CKA, it has been suggested that carborane derivatives suppress HIF-1α which is strongly involved cancer metastasis. Therefore, we evaluated the metastasis inhibitory effect of melanoma by CKA. Furthermore, Kojic acid is known as glucose metabolite of koji mold. Therefore, we estimated and evaluated that CKA having kojic acid is transferred into the cell via the glucose transporter.

[Material&Method]
Cytotoxicity of CKA/HP-β-CD on melanoma, mouse rectal cancer cells, myoblasts was

evaluated by WST assay. After Bio-distribution of CKA/HP-β-CD toward melanoma bearing mice was estimeted, neutron irradiation was performed at 5 MW 18 min (total fluence: 5.0 × 1012 n•cm-1) at the Kyoto University Research Reactor, then, BNCT evaluation on anti-tumor effect was performed. Inhibition of HIF-1α expression of CKA was evaluated by Western blotting under hypoxic conditions. The ability of CKA to inhibit metastasis was evaluated for migration ability by scratch assay in cultured cells and metastasis inhibitory ability by real time PCR for tumor bearing mice. In the experiment of mechanism with the internalization of CKA, afetr knockdown of glucose transporter 1 (GLUT1) by siRNA or inhibition of GLUT1 by WZB117, incorporation of CKA by melanoma cells were evaluated.

[Result]
We succeeded in solubilizing CKA by 55% effciacy with 8800 ppm of boron concentration. Higher incorporation of CKA with melanoma cells was confirmed compared with mouse rectal cancer cells and myoblasts cells. In the pharmacokinetics evaluation, the highest concentration and accumulattion compared to normal cells was observed after 1 hour of administeration, and tumor selectivity was confirmed. In addition, in the evaluation of BNCT, a concentration-dependent survival benefit and an inhibitory effect of metastasis of melanoma cells toward lung were obtained. By using CKA/HP-β-CD complex, expression of HIF-1α, subclass of HIF-1, was suppressed with concentration of CKA in HeLa cells. From the results of scratch assay, it was found that CKA suppressed the migration of melanoma cells. Furthermore, from the results of real-time PCR, suppression of melanoma metastasis was confirmed in mouse organs of the CKA administered group as compared with PBS administered group mice. CKA significantly suppressed melanoma metastasis to the brain, among other organs. Since the incorporation of CKA/HP-β-CD complex strongly supressed with the knockdown of glucose transporter 1 (GLUT1) by siRNA and the inhibition of GLUT1 by WZB117, CKA migrates into melanoma cells via glucose transporter 1 was signifficantly suggested.

[Conclusion]
the water-solubility of CKA which is expected to have selectivity for melanoma was strongly improved by supramolecular formation by using cyclodextrin. From results including cellular and animal experiments, it was shown that CKA is potent for not only a BNCT drug but also a melanoma metastasis inhibitor.

Keyword: Kojic acid-modified carborane, Hydroxypropyl-β-cyclodextrin, melanoma, inhibitor

PS2 Ch 03

Development of S-Alkyl-closo-Dodecaborate-Containing Amino Acids as Boron Carrier for BNCT

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Introduction
In the development of useful boron carriers for BNCT, unusual boron amino acids represented by L-p-boronophenylalanine (BPA) have long being recognized as tumor seeking compounds due to structural analogy to usual L-amino acid, because L-amino acid transport system (LAT1) is enhanced compared with normal tissues to sustain the proliferation of tumor cells. On the other hand, dodecaborate ([B12H12]2-), the mother nucleus of mercapto-closo-dodecaborate (BSH) is a versatile and available boron cluster bearing high boron occupancy. In the course of our developing studies on new boron carrier for BNCT, we have designed and synthesized thiododecaborate ([B12H11S]2-) unit-containing L-amino acids, a new class of tumor seeking and water soluble amino acid. Especially, medium-chain alkyl sulfoniododecaborate ([B12H11S+R]-; R=octyl, decyl, dodecyl) unit containing amino acids showed high cell membrane permeability, low cytotoxicity and high water-solubility, and these compounds could deliver large amount of boron to several kinds of tumor cells. Here, we present the synthesis of novel medium-chain alkyl sulfoniododecaborate containing amino acids. Furthermore, we report the biological evaluation of boron compounds as boron carrier for BNCT.

Material and Method
We designed and synthesized two types of S-alkylthio-closo-dodecaborate ([B12H11S+R]-; R=octyl, decyl, dodecyl) unit containing α-amino acids on their side chain {[B12H11SR]1--(C2H4)-CH(NH2)COOH, I} or C-terminal {[B12H11SR]1- propyl-NH2CO-CHR(NH2), II} by S-alkylation reaction of S-alkyl-BSH in moderate yield. To evaluate the I and II, we examined the cytotoxicity test (WST-8), boron accumulation test for tumor cells, micro-distribution analysis, etc.

Results and Discussion
The water solubility of I and II was higher than that of BPA. The cytotoxicity of I and II was marginally low (IC50 of I and II is 0.1 mM in C6 glioma and B16 melanoma cells).

In the next step, we measured the boron concentrations in tumor cells by ICP-OES. Compound I and II were uptaken in tumor cells, and these were localized in the cytosol and excluded from the cell nucleus. The intracellular boron concentration of I and II in C6 and B16 cells was 2-3 times greater than that of L-BPA, with fewer doses of the compounds. Furthermore, cell-uptake of compound I and II were inhibited by the neutral amino acids. These results suggested that these dodecaborate amino acids might be a potential lead compounds to develop novel boron compounds for BNCT.

Keyword: dodecaborate, S-Alkyl-closo-dodecaborate, boron-containing amino acid

PS2 Ch 04

Preparation methods of liposome which encapsulated boron compound at high concentration and efficiency.

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[Introduction]
Properties required as a boron compound for Boron Neutron Capture Therapy (BNCT) are as follows. i) 10B concentration of at least 20 ppm or more can be achieved in a tumor. ii) Meanwhile, 10B concentration is as low as possible in normal tissues. iii) A tumor/blood ratio is preferably 5-10 or higher. Recently, as a means to accumulate boron compound, method of boron delivery using DDS (Drug Delivery System) is remarkable in BNCT. A liposome is widely used as DDS material and can encapsulate drugs in the inner layer. The aqueous layer can introduce the water soluble compounds and the lipid bilayer membrane can introduce the lipophilic compounds. Therefore, a lot of studies to encapsulated drugs into liposomes are reported. In the BNCT study, Hawthorne tried to encapsulate various boron compounds into liposomes and measure the encapsulation ratio of it. However, the encapsulation ratio was very low. We have attempted to improve boron concentration by various encapsulation methods of boron compounds into liposome. And also, we evaluated physical property of liposome which prepared at high boron concentration.

[Material and Methods]
Each lipids (Distearoylphosphatidylcholine, Cholesterol, DSPE-PEG) prepared at the constant ratio were dissolved in organic solvent (chloroform, methanol) and liposome was prepared using it by the lipid-film method. Boron compounds (BSH or BPA) were encapsulated to liposome by ultrasonic treatment methods, freeze-thaw method or reverse-phase evaporation method. The resulting liposomes were extruded with an extruder through a polycarbonate membrane with a 100-nm pour size, yielding the boron liposome. As for these liposomes, we measured the boron concentration by ICP-OES (Inductivity coupled plasma optical emission spectrometer) and calculated the efficiency of boron compounds which encapsulated into liposome. Furthermore, we validated stability of the drug formulation by observing a leakage rate of the boron compounds under serum-containing medium at 37 degrees condition until 48 hours.

[Results]
Compared with each encapsulation methods, boron concentration of liposomal inner layer did not offer significant improvement over, but encapsulation rate improved by increasing the lipid concentration. The encapsulation efficiency of BSH improved to 32.7% from 4.2% when it prepared bare liposome at 100mg/mL lipid concentration. The liposome that was constructed by high boron concentration did not almost leak the inner boron compound in observation less than 48 hours, and extremely high stability was suggested.

[Conclusion]
We succeeded in development of preparation method of a liposome encapsulating boron compounds at high boron concentration and efficiency. These results suggest that the preparation method of a liposome is useful for development of high boron assembly. Therefore, this method will lead to deliver much boron when boron compounds encapsulated into liposome which modified with various compound (ex. protein, antibody, peptide, et al.) to the outer layer.

Keyword: Liposome, DDS, Encapsulation

PS2 Ch 05

Development of boron-loaded Microbubbles for Focused Ultrasound Triggered Brain Tumor Drug Delivery

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Abstracts Posters

Introduction
Boron neutron capture therapy (BNCT) is the mainstay radiotherapy for treating glioblastoma multiforme (GBM). However, the penetration of current clinical drug (i.e. BSH) for BNCT into brain tumor is limited by the cerebral vesicular protective structures, blood-brain barrier (BBB) and blood-tumor barrier (BTB). In order to achieve sufficient tumor/normal tissue (T/N) ratio of BSH for BNCT treatment, it is necessary to wait BSH natural diffusion into tumor for several hours (~6 h) via ERP effect, probably inducing greatly different deposition within tumor. This study proposed the boron drug (PEG-b-PMBSH) loaded cationic microbubbles (B-MBs). With focused ultrasound (FUS) sonication, B-MBs could simultaneously achieved BBB-opening and boron drug delivery into tumor tissue, improving the T/N ratio in 30 min.

Material and Method
B-MBs (5.5 ppm) were prepared by loading PEG-b-PMBSH (300 ± 9 nm) onto the lipid-shell of cationic MBs (1 ± 0.2 μm) by electrostatic force. Eighteen GL261 glioma cells implanted C57BL/6 mice were used. On day 14 after the tumor cells implantation (tumor volume of 38 ± 9 mm3 estimated by MRI T2W imaging), FUS (frequency = 1 MHz, energy = 0.3-0.7 MPa, duty cycle = 0.5%, sonication = 1 min) was applied following B-MB IV injection. The permeability of BBB was estimated by Evans blue staining. The B10 deposition within tumor tissue were quantified and mapped by inductively coupled plasma mass spectrometry (ICP-MS) and laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS), respectively.

Result
B-MBs with FUS (0.5 MPa) provided sufficient BBB-opening area for enhanced Evans blue within tumor lesions without occurrence of brain damage. Compared with the group of MBs with PEG-b-PMBSH separately administration, the T/N ratio was immediately increase into the tumor by B-MBs (3.8 ± 0.017 vs 1.3 ± 0.001) within 30 min. In addition, the tumor/blood tissue (T/B ratio) were largely increase following the encapsulation of PEG-b-PMBSH into MBs (1.4 ± 0.3 vs 0.08 ± 0.01). The LA-ICP-MS also confirmed that the treatment of B-MBs with FUS not only enhanced the permeability of BBB, but also largely delivered 10B into the tumor.

Conclusion
The T/N ratio could be improved 3 fold by the proposed drug delivery platform within 30 min. The Boron concentration within blood could be decreased 20 fold by the encapsulation of MBs. Future work including: (1) increasing the amount of drug accumulation (elongating the FUS irradiation time and improving the amount of drug encapsulation); (2) combing with BNCT for brain tumor treatment with low side-effects.

Keyword: Boron neutron capture therapy (BNCT), Microbubble (MBs), Focus Ultrasound (FUS), Blood brain barrier

PS2 Ch 06

Synthesis and investigation of carborane coumarins as potential agents for BNCT

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There are very few boron-containing products identified to date to serve as leads for medicinal chemists. However, physical, chemical and biological properties of boron offer medicinal chemists a rare opportunity to explore and pioneer new areas of drug discovery. Boron therapeutics are emerging that show different modes of inhibition against a variety of biological targets. The occurrence of this class of compound is likely to grow over the next decade and boron could become widely accepted as a useful element in future drug discovery.
Polyhedral heteroboranes are unique objects of intense research of the present day. A subset of this extensive class of compounds are carboranes having the general formula C2B10H12. Since the discovery of carboranes in 1963 various applications have been found in catalysis, materials design, and medicine. Over the past decade, there has been an increasing interest in the use of carboranes as pharmacophoric units in drug design. The role of carboranes in medicinal chemistry extends into areas of drug discovery, molecular imaging, targeted radionuclide therapy, chemo therapy, and boron-neutron capture therapy (BNCT).
At the same time, various coumarin derivatives are used in clinical practice, mainly as anticoagulants [24-26], however, synthesis and investigation of coumarin-hybrids is an actual task today since they have a wide range of therapeutic activity: antioxidants, anti-inflammatory, antitumor, MAO-B inhibitor, antimicrobial and antimalarial [27-30]. The multifunctionality of these hybrid compounds makes them potential candidates for drugs for the treatment of multifactorial diseases such as cancer, Alzheimer's disease, metabolic

Abstracts Posters

syndromes, AIDS, malaria and cardiovascular diseases. Thus, study of synthesis ways of carbarane derivatives of coumarins can open a new prospects in the preparation of drugs with wide biological activity include anticancer activity.
In this research, different carborane derivatives of coumarins, nitroalkanes, hydrindones were synthesized. All compounds were characterization by FTIR, NMR 1H, 11B. In vitro tests shown low toxicity of synthesized compounds. Further we plan to continue the study of toxicity, biological activity and distribution of boron compounds between normal and cancer cells.

Keyword: carborane, coumarin, synthesis, BNCT

PS2 R 09

In vitro studies of the DNA damage response (DDR) induced by BNCT

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Introduction: The radiation field produced in the tumor during the application of BNCT is a mixture of high and low LET components which activates the DNA damage response (DDR) including double strand break (DSB) repair and cell death by mitotic catastrophe or apoptosis. It is well known the role of TGF beta1 in homoeostatic growth control; however it has been less studied its complex role in regulating responses to genotoxic stress through transcription factors Smad. The aim of these studies was to analyze the TGF beta / Smad signaling pathway as part of the DDR arising from BNCT and the cross-talk between members of the different pathways. Materials and Methods: HT29 human colon cancer cells were seeded in bottles of 25cm2 and irradiated in exponential phase of growth. Then the cells were distributed in 4 groups: 1) Control; 2) BNCT (BPA + neutrons); 3) NCT (neutrons alone) and 4) Bystander effect from BNCT. BPA was used in a concentration of 0.925 mM (10ppm 10B) and irradiation was carried out in RA3 reactor (Neutron flux of 1.1010 n / cm2sec) in order to obtain a total absorbed physical dose of 3 Gy. After irradiation the cells were incubated for 1.5 hours in an oven at 37◦ C. In order to study the mRNA of TGF beta1, Smad2 Smad7 and ATM, the total RNA was extracted with Trizol and real time PCR was performed for each gene. Results: the expression of TGF beta1 and Smad7 increased in all the irradiated groups respect to the Control group. For TGF beta1, this increase was greater in the group irradiated with neutrons alone (NCT) than for the BNCT group. The indirectly irradiated group (Bystander) behaved in a way similar to the NCT group. The results obtained for Smad7 showed an increase larger for BNCT than for NCT group compared with Control. The expression of Smad2 decreased respect to the Control in all the irradiated groups, being greater for NCT and Bystander than for the BNCT group. ATM shows a decrease in all treated groups with respect to the Control group. Conclusions: The increase in the expression of TGF beta and Smad7 on the one hand, and the decrease of Smad2 on the other, for all the groups irradiated would be consistent with the decrease in cell survival previously observed by our group. The increased expression of Smad7 would act by inhibiting this pathway through the blockade of Smad2 and therefore increasing the genetic instability, which would result in a greater number of chromosomal aberrations and cell death. The decrease observed in the expression of ATM could be due to an increase in ATR which would mediate the double chain damage response (DDR). The description of the mechanisms will allow studying strategies of manipulation of the cellular response with potential translation to the clinic.

Keyword: BNCT, TGFbeta1, pathway, DNA damage response

PS2 R 10

Evaluation of beta-emitting devices as a complementary tool of BNCT for the treatment of superficial cancer

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Introduction: BNCT clinical trials in Argentina restarted in 2015 after modifications in the beam at RA6 reactor. Due to the neutron beam characteristics, the maximum dose is not on the surface of the tumour but at 1cm centimeter deep. Materials such as rhodium, silver and indium have high-energy beta particles emission, a large neutron capture cross section and rapid decay activation products. As beta radiation has a short range on tissue these devices named beta enhancers (BE) can be used to compensate or even significantly increase the surface dose gradient during a BNCT treatment. In previous studies we demonstrated that nude mice, bearing surface tumours and irradiated by BNCT with the addition of rhodium BE devices showed no signs of toxicity and effectiveness to control the tumour growth.

Objective: Evaluation of radiotoxicity and effectiveness of three BE devices (rhodium, silver and indium) as a complementary tool of BNCT.
Materials and Methods: Sixty NIH nude mice (25-30 g body weight) were implanted subcutaneously with cells from the HT-29 colon cancer human cell line, developing tumours between 150 and 200 mm3 of size at day 15. The animals were divided into 4 groups: 1) Control; 2) BNCT + BE rhodium; 3) BNCT + BE silver; 4) BNCT + BE indium. Animals of groups 2, 3 and 4 received 350 mg/kg of body weight of borophenylalanine (10BPA). The mice received subcutaneous anesthesia and were irradiated at a specific positioning for 42.5 minutes with a neutron flux of 4.96 x 108 n/cm2sec. The animal's body weight and the tumor growth were evaluated. Also histological and immunohistochemical studies were performed.

Results: The animal did not show any signs of radiotoxicity (body weight during the time of evaluation). Some animals in group 4 showed mild erythema in the tumor area, which reverted after the first week. Complete inhibition of tumor growth was observed in the three BNCT-BE groups during the first three weeks. The histological studies performed at seven days showed a lower percentage of the viable area (taking in account the tumour volume) in the three treated groups, being even lower for the group 4. The analysis of cells in mitosis process showed that the number of cells was lower in the three treatments. The number of vacuoles as an indicator of death cell by autophagy showed a high value for the three BNCT groups being larger for group 4. The CD133 and CD166 positive cells indicated the presence of cancer stem cells (CSCs) in the viable area of the tumour. Its persistence, although diminished, a week after irradiation, would seem to be associated with tumour proliferation and loss of control over the growth of tumour with any of the devices used. The total physical doses absorbed by the tumours did not show significant differences between the three irradiated groups and were of 7.31 Gy for BNCT-Rh, of 7.34 Gy for BNCT-Ag and of 6.59 Gy for BNCT-In.

Conclusions: These studies demonstrated that the three devices would be non-toxic and effective as complementary tools to BNCT for the treatment of superficial tumours. At the macroscopic level, no significant differences in tumour growth were observed among the three groups. However, at the microscopic level with the BE of Indium, a greater biological effect was obtained. To understand the higher cell damage observed with BE of Indium, the radiochemical processes involved will be studied.

Keyword: BNCT, Beta enhancers, Cancer stem cells.

理未易察
Truth is not easy to be understood

International Congress on Neutron Capture Therapy
ICNCT 18th
Taipei, Taiwan
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Author Index

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
ABO	Keisuke		Rotary Type Beam profile monitor for Accelerator-Driven BNCT System	PS2 P 06
AIHARA	Teruhito		BNCT for Head and Neck Cancer : Summary of reactor irradiation.	Pa Cl1 03
AKABORI	Kiyotaka		A real-time neutron monitor for BNCT	Pa P1 03
AKITA	Kazuhiko		Evaluation of neutron measurement system utilizing a LiCAF scintillator - optical fiber detector	PS2 P 04
AKITA	Kazuhiko		Installation of accelerator-based BNCT system at Kansai BNCT Medical Center	PS2 P 05
ANDOH	Tooru		Preclinical study on boron neutron capture therapy for bone metastasis with human breast cancer cell lines	Pa Ch1 02
ANDOH	Tooru		Gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs) for neutron capture therapy of cancer: Influence of particle size of Gd-nanoCPs on tumor-killing effect in vitro	PS1 Ch 06
ANIKIN	Mikhail		Feasibility study of using IRT-T research reactor for BNCT applications	PS1 P 01
ARAI	KAZUHIRO		Evaluation of a newly developed water-equivalent bolus technique in accelerator-based boron neutron capture therapy for skin tumors	PS1 P 15
AUTERINEN	Iiro		BEAM DOSIMETRY EQUIPMENT FOR THE NUBEAM BNCT SUITE AT HELSINKI UNIVERSITY HOSPITAL CANCER CENTER	PS2 P 18
BABA	Kentaro		Calculation of the response matrix of a PMMA cylindrical neutron spectrometer in consideration of angle distribution	PS1 P 09
BEDOGNI	Roberto		Opportunities for therapeutic beam monitoring with single-moderator spectrometers	Pa P5 05
BYKOV	Timofey	Aleksandrovich	Data processing automatization and improvements of D-Pace OWS-30 wire scanner	PS1 P 02
BYKOV	Timofey	Aleksandrovich	Visualization of a negative hydrogen ions beam in a vacuum insulation tandem accelerator	PS1 P 03
CHANG	Hyegang		Beam characteristics and in phantom dosimetry for accelerator-based boron neutron capture therapy: Comparative study of Monte Carlo simulations using Geant4 and MCNP6	Pa P2 01
CHEN	XINRU		Neutron Beams Optimization of Nuclear Medical Ship	PS1 P 08
CHEN	Lichao		The role of GM-CSF during early cellular responses after BNCR and gamma irradiation	PS1 R 02
CHEN	Jen-Kun		Cellular uptake of BPA: homogeneous or heterogeneous in a population of cells	PI Ch 03
CHOU	Fong-In		The specific retention of boric acid in liver tumor for BNCT in a single liver tumor-bearing rat and a multifocal liver tumor-bearing rabbit models	PS1 B 02
CHOU	Fong-In		The therapeutic efficacy and radiobiological effects of boric acid-mediated BNCT in a VX2 multifocal liver tumor-bearing rabbit model	PI R 02
CHUANG	Yung-Jen		Zebrafish as a cancer model system for neutron capture therapy research	PI M 02
DAGROSA	Maria	Alejandra	In vitro studies of the DNA damage response (DDR) induced by BNCT	PS2 R 09
DAGROSA	Maria	Alejandra	Evaluation of beta-emitting devices as a complementary tool of BNCT for the treatment of superficial cancer	PS2 R 10
DOWAKI	Satoshi		Functional evaluation of kojic acid-modified carborane developed as a boron drug for melanoma BNCT	PS2 Ch 02
FATEMI	Setareh		Simulations of an imaging system based on a CZT photon detector for a future BNCT-SPECT.	PS1 B 03
FATEMI	Setareh		Response of a CZT detector to the neutron and gamma radiation field of an accelerator based BNCT facility.	Pa B2 04
FEINER	Irene	Veronika Judith	Synthesis and radiolabelling (124I) of multifunctionalised gold nanorods (AuNRs) as boron drug delivery agents using a pretargeting strategy based on bioorthogonal 'click reaction' with application in Boron Neutron Capture Therapy.	Pa Ch1 03
FU	Shinian		D-BNCT Project in China	Pa Ph6 02
FUJIMOTO	Takuya		Study on application of BNCT to synovial sarcoma	PS2 Cl 03

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
FUKUDA	Hiroshi		B-10 concentration kinetics in the tumor and blood in patients administered with BPA: a critical review	Pa Cl2 07
FUKUDA	Hiroshi		Fundamental and pioneering achievements in basic and clinical study for BNCT	Pl Cl2 01
FUKUMURA	Masao		5-aminolevulinic acid can sensitize malignant glioma to boronophenylalanine-based boron neutron capture therapy	Pa R2 01
GAMBARINI	Grazia		Uncertainties in the absorbed dose determination in irradiations with epithermal neutrons due to the dependence of neutron transport on shape and size of the exposed volume	Pa P1 09
GARABALINO	Marcela	Alejandra	Electroporation to optimize boron targeting for Boron Neutron Capture Therapy (BNCT): a study of boron biodistribution with Boric Acid in the hamster cheek pouch oral cancer model	Pa R1 02
GARABALINO	Marcela	Alejandra	Biodistribution of Boric Acid (BA) and Boronphenylalanine (BPA) for BNCT in the hamster cheek pouch oral cancer model	PS2 R 01
GENINATTI CRICH	Simonetta		An innovative therapeutic approach for malignant mesothelioma treatment based on the use of Gd/Boron multimodal probes for MRI guided BNCT	Pa Ch3 03
GONZALEZ	Sara	Josefina	How do photon iso-effective tumor doses derived from in-vitro BNCT studies compare to those from in-vivo cancer model data?	Pa P3 06
GONZALEZ	Sara	Josefina	Extension of the photon iso-ffective dose model to the dose-limiting normal tissues for BNCT of head and neck cancer	Pa P3 07
GRYZINSKI	Michal	Aleksander	BNCT FACILITY AT MARIA REACTOR – FINAL KICK-OFF: BEAM TEST, OPENING RESEARCH STATION, CONSTRUCTION OF BUILDING FOR REACTOR LABORATORY FOR BIOMEDICAL RESEARCH AND PROGRESS IN FORMULATION PROGRAMME OF "NEOBOR" SCIENTIFIC PLATFORM	Pa P5 03
GUAN	Xingcai		High-accuracy measurement of the epithermal neutron flux of a 7Li(p,n)7Be-based BNCT neutron source with activation monitors	PS2 P 12
HARADA	Takaomi		Influence of oxygen status on therapeutic effect of boron neutron capture therapy in human tumor cells	PS2 R 08
HATTORI	Yoshihide		Development of S-Alkyl-closo-Dodecaborate-Containing Amino Acids as Boron Carrier for BNCT	PS2 Ch 03
HE	Guozhu		Study of neutron production and moderation for Sulfur Neutron Capture Therapy	Pa Ph6 03
HERVE	Marine		Neutron field characterization for Neutron Capture Therapies	PS2 P 01
HINOTO	Ryoichi		Dosimetric influence of respiratory motion in boron neutron capture therapy for plumonary tumor	Pa P4 02
HIRAGA	FUJIO		Monte Carlo simulation-based design for an electron-linac-based neutron source for boron neutron capture therapy	PS2 P 02
HIRATSUKA	Junichi		Boron neutron capture therapy for vulvar melanoma and extramammary Paget's disease of the genital regions	Pa Cl2 01
HIROSE	Katsumi		How much does tumor location affect the treatment field size passively determined by a dose constraint to the mucosa inhead and neck boron neutron capture therapy?	Pa Cl2 08
HORI	Hitoshi		Boron Tracedrugs: Drug-Design Challenge For Neutron Dynamic Therapy	PS1 Ch 01
HU	Naonori		Neutron beam quality measurement of accelerator-based neutron source using microdosimetric technique	Pa P2 03
HUANG	Nai Chun		Recycling 10B-enriched Boronophenylalanine in Urine of Patients with Recurrent Brain Tumor	PS1 Cl 02
HUANG	Li-Wen		Treatment Result of Combined Volumetric-Modulated Arc Therapy (VMAT) and Simultaneously Integrated Inner-escalated Boost (SIEB) Radiotherapy in a Patient with Locally Advanced Maxillary Sinus Carcinoma.	PS2 M 02
HUANG	Jung Yun		Design of Neutron Moderation Assembly for A-BNCT	PS2 P 07

Author Index

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
HWANG	Jeng-Jong		Using Promoters of Granzyme B or NF-kB driven reporter genes combined with Multimodalities of Molecular Imaging for Theranostics of BNCT	Pl R 04
ICHIKAWA	Go		Development of Thermal Neutron Moderator for Testing Boron Agents for Boron Neutron Capture Therapy (BNCT)	PS1 P 16
IGAKI	Hiroshi		Comparison between SUVmax, TNR, and TBR in 18F-BPA PET. Which index is correlated best with 18FDG uptake?	Pa Cl1 05
IGAWA	Kazuyo		In vivo Evaluation system for accelerator-based Boron Neutron Capture Therapy	Pl M 01
IMAMICHI	Shoji		Investigation of the biological properties of neutron beam of accelerator-based BNCT system with intestinal crypt regeneration and ICP-AES	PS2 R 07
ITOH	Taiki		Development of Boron-Containing Monosaccharide Derivatives for Boron Neutron Capture Therapy	Pa Ch2 03
JIANG	Shiang-Huei		The overview and prospects of BNCT facility at Tsing Hua Open-pool Reactor	Pa M1 09
KANEMITSU	TAKUYA		Evaluation of folate receptor targeted novel boron compound for boron neutron capture therapy using rat brain tumor model	Pa R2 02
KATO	Itsuro		Boron neutron capture therapy in 45 patients with recurrent head and neck cancers who have no other treatment options.	PS1 Cl 03
KATO	Takahiro		Quality assurance of an accelerator-based boron neutron capture therapy system: Dosimetric and mechanical aspects based on initial experience	PS1 P 14
KATO	Ryohei		Preliminary study of the impact on dose distribution due to the reproducibility of shoulder position in sitting-positioned BNCT for head and neck cancer	PS2 Cl 01
KAWABATA	Shinji		Successful result in Overall Survival from Phase II Clinical Study of BNCT with XRT/TMZ in Patients with Newly Diagnosed Glioblastoma	Pl Cl1 02
KAWAI	Kazuki		Development of cyclic RGD-functionalized maleimide-containing closo-dodecaborate albumin conjugate (MID-AC) as an active tumor targeting boron carrier for neutron capture therapy	PS1 Ch 05
KICHIGIN	Aleksandr	Ivanovich	Radiobiological in vitro and in vivo investigations on accelerator neutron source in Budker Institute of Nuclear Physics	Pa R1 04
KINASHI	Yuko		The combination effect of neutron irradiation and exposure to DNA-alkylating agent on glioblastoma cell lines with different MGMT and p53 status	PS1 R 04
KIRIHATA	Mitsunori		Synthetic study on [18F]–L-2-fluoro-4-boronophenylalanine (18FBPA), a theranostic compound in BPA BNCT, by “F minus method”	Pl Ch 04
KIYANAGI	Yoshiaki		Effect of fast neutron and gamma-ray ratios on a dose distribution in a water phantom	Pa P2 09
KOBAYASHI	Tooru		A practical handling of the limitation of absorbed dose in BNCT	Pa M1 01
KOIVUNORO	Hanna		Comparison of relative biological effectiveness (RBE) doses and the photon iso-effective dose model for predicting the normal tissue complication probability in boron neutron capture therapy (BNCT) of head and neck cancer patients	Pa P3 03
KONDO	Natsuko		Uptake of p-borono-phenylalanine by brain tumor stem cells analyzed by mass cytometry	Pa B2 02
KOROLKOV	Ilya	V	Synthesis and investigation of carborane coumarins as potential agents for BNCT	PS2 Ch 06

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
KUMADA	Hiroaki		Verification for dose estimation performance of a Monte-Carlo based treatment planning system in University of Tsukuba	Pa P2 07
KUMADA	Hiroaki		Development of a novel patient setting & real-time monitoring system using motion capture technology for boron neutron capture therapy	Pa P2 08
Lai	Bo-Lun		Comparison of Shielding Calculation Methods for an AB-BNCT Facility Based on the Be(p,xn) Reaction with 30 MeV Protons	Pa P5 04
LAN	Tien Li		Salvage Boron Neutron Capture Therapy (BNCT), Treatment Experiences of Recurrent Malignant Brain Tumors in Taiwan	Pa Cl1 01
LEE	Kuo Wei		Design of a model for BSA to meet free beam parameters for a 3.5 MeV linear accelerator	PS1 P 12
LEE	Kuo Wei		Development of a treatment planning system for BNCT	PS1 P 13
LEE	Yi-Jang		188Re-liposome, a high energy beta-particle radiopharmaceutical shows enhanced efficacy on suppression of head and neck squamous cell carcinoma progression by repeated doses	PS1 R 03
LI	Ming-Hsin		In Vivo Imaging Evaluation of a Neuropeptide (NPY) Derivative Containing Boron-rich for Breast Tumor Therapy	Pl Ch 02
LI	Yan		Physical Design of Modular Neutron Source Device for AB-BNCT	PS2 P 11
LIN	BO-RONG		Characterization Study of Boron-10 Doped Nanodiamonds Made by Ion Implantation	Pa P2 04
LIN	BO-RONG		A New Boron Delivery Agent: Boron-10 Doped Nanodiamonds Made by Ion Implantation	Pa P2 05
LIN	Chi-Shuo		Reirradiation of Locally Recurrent Head and Neck Cancer with BNCT or Proton Therapy: a Systematic Review	PS1 Cl 01
LIN	Ko-Han		Initial experience of using a hybrid PET/MRI scanner for FBPA-PET	Pl Cl2 03
LIU	Zhibo		A novel boron-derived tyrosine serves as a theranostic agent for positron emission tomography and boron neutron capture therapy	Pa Ch3 01
LIU	Zhibo		Rational Designed Boronated Porphyrin Loaded Micelle Meet the Shortcoming of Small Molecule Boron Agents for Boron Neutron Capture Therapy	Pa Ch3 02
LIU	Yuan-Hao		The Design of the Xiamen Humanity Hospital BNCT Center	Pl P2 02
LU	Wei-hua		The influences of moderator geometry on beam quality of Li-target based AB-BNCT	Pa P4 04
MAGNI	Chiara		Design of a BNCT irradiation room based on proton accelerator and Be target	Pa P3 02
MALIMBAN	Justin		Monte Carlo Simulation and Experimental Characterization of Tissue Equivalent Proportional Counter (TEPC) for Neutron Dosimetry	Pa P1 06
MASUI	SHIN		Current Status of BNCT Clinical Trials in Japan	Pa M1 05
Masunaga	Shin-ichiro		Effect of the change in a reactor power on the response of murine solid tumors in vivo, also referring to that in quiescent tumor cells, and its clinical significance in boron neutron capture therapy (BNCT)	Pl R 01
MASUTANI	Mitsuko		The biological properties of BNCR and accelerator-based BNCT system installed in NCC	Pl R 03
MATSUMOTO	Yoshitaka		Folate-modified cyclodextrin improves the intratumoral accumulation of existing boron compounds.	PS1 R 01
MICHAS	Edyta		REACTOR LABORATORY FOR BIOMEDICAL RESEARCH IN THE NATIONAL CENTRE FOR NUCLEAR RESEARCH, POLAND	Pa M1 08
MICHIUE	Hiroyuki		New self-assembling peptide Drug Delivery System with BSH toward clinical application	Pa Ch2 01
MIYATAKE	Shin-Ichi		Results of phase 1 clinical trial of accelerator-based BNCT for recurrent malignant gliomas	Pa Cl1 02
MIZUMOTO	Tetsuya		Development of the electron tracking Compton camera for on-line imaging of 478 keV prompt gamma rays in BNCT	Pa B2 03
MONTI	Valeria		e_LiBANS project: thermal and epithermal neutron sources based on a medical Linac	Pa P4 03

Author Index

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
MONTI HUGHES	ANDREA		OPTIMIZATION OF THE CLASSICAL CHEMICAL CANCERIZATION PROTOCOL IN THE HAMSTER CHEEK POUCH TO STUDY BNCT FOR ORAL CANCER	PS2 R 02
MONTI HUGHES	ANDREA		NOVEL ORAL CANCER & PRECANCER EXPERIMENTAL MODEL FOR SIMULTANEOUS LONG TERM EVALUATION OF THE EFFECT OF BNCT ON TUMORS AND PRECANCEROUS TISSUE	PS2 R 03
MONTI HUGHES	ANDREA		RADIOTOXICITY INDUCED BY BNCT MEDIATED BY BPA: A COMPARATIVE ANALYSIS IN AN ORAL CANCER MODEL EMPLOYING THREE DIFFERENT CANCERIZATION PROTOCOLS	PS2 R 04
MONTI HUGHES	ANDREA		BIODISTRIBUTION STUDIES OF MALEIMIDE-FUNCTIONALIZED CLOSO-DODECABORATE ALBUMIN CONJUGATES (MID:BSA) IN THE HAMSTER CHEEK POUCH ORAL CANCER MODEL	Pa R3 01
MONTI HUGHES	ANDREA		EVALUATION OF THE RADIOPROTECTIVE EFFECT OF OLIGO-FUCOIDAN TO REDUCE DERMATITIS AND MUCOSITIS INDUCED BY BNCT IN ORAL CANCER AND ECTOPIC COLON CANCER MODELS	Pa R3 02
MOTOYANAGI	Tomoaki		Evaluation of the impact on a change of patient's posture from preplan with diagnostic images to treatment position in boron neutron capture therapy	PS1 Cl 04
MUKAWA	Tetsuya		Development status of BNCT Treatment Planning System: SACRA planning	Pa P2 02
MUNEVAR	Edwin		ADVANCES OF THE CHARACTERIZATION OF NEUTRON CAPTURE BY BORON AND GADOLINIUM USING GEANT4	PS2 P 09
NAKAI	Kei		Boron analysis and imaging of 2hr-BPA-exposured cells by using micro proton particle induced gamma-ray emission (PIGE).	Pa B1 02
NAKAMURA	Satoshi		Neutron control method for an accelerator-based BNCT system with a solid-state Li target	PS1 P 06
NAKAMURA	Hiroyuki		Development of closo-dodecaborate-containing water-soluble folate derivatives targeting to folate receptor α for boron neutron capture therapy	Pa Ch2 02
NAVASCUEZ	Marcos		Boron-rich oil-in-water emulsions as drug nanocarriers for boron neutron capture therapy	PS2 Ch 01
NOMOTO	Takahiro		Metabolism-controlled boron delivery systems composed of p-boronophenylalanine and poly(vinyl alcohol)	Pa Ch1 01
OGALLAR RUIZ	Francisco		Study of the role of neutron induced nuclear reactions on chlorine in healthy tissue dosimetric calculations for BNCT. Measurement of their cross sections at n_TOF (CERN).	Pa P1 07
OHMAE	Masatoshi		Treatment of Major Cervical Artery Invasion of Head and Neck Cancer with Boron Neutron Capture Therapy	PS2 Cl 04
OHNISHI	Ken		Overexpression of LAT1 by lipofection enhances BPA intracellular incorporation in glioblastoma cells	PS1 R 06
OKAZAKI	Keita		Development of a prompt gamma ray imaging detector using LaBr3(Ce) scintillator and arrayed MPPC for Boron Neutron Capture Therapy	Pa B2 01
OLIVERA	Maria	Silvina	Biological evaluation of boric acid uptake at different administration times. Comparative study between BPA and BA accumulation curves.	PS1 R 05
PAN	Po-Shen		Bio-distribution of Boron-containing Oligopeptide/Depsipeptide Analogs using DAHMI Tagging System	Pl Ch 01
PANZA	Luigi		Dodecaborate-sugar conjugates as delivery system for BNCT	Pa Ch2 04
PEDROSA RIVERA	Maria		Radiobiology experiments for thermal and epithermal RBE factors in BNCT	Pa R2 03
PIESTRUP	Melvin	A	A High Flux Thermal Neutron Source for Small Animal Models for the Development of Drugs for Boron Delivery to Cancer Sites	PS1 P 07
PORRA	Liisa		COMMISSIONING OF THE NUBEAM BNCT NEUTRON SOURCE AT HELSINKI UNIVERSITY HOSPITAL CANCER CENTER	Pa P1 10

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
PORRAS	Ignacio		Study of the potential application of low energy neutrons from neutron guides to BNCT radiosurgery	PS1 P 05
PORRAS	Ignacio		In vitro studies of new boron-rich nanostructures for BNCT	PS1 Ch 04
PORRRAS	Ignacio		Some open problems for the improvement and the expansion of BNCT	Pl P2 01
PORTU	Agustina	Mariana	Neutron autoradiography combined with UV-C sensitization: towards intracellular localization of boron	Pa B1 03
PORTU	Agustina	Mariana	Neutron autoradiography approaches to study microdistribution of boron compounds in a diffuse lung metastases experimental model	Pa B1 04
PORTU	Agustina	Mariana	Microfluidic technology for the synthesis of liposomes encapsulating boron compounds in Argentina	Pa Ch2 05
POSTUMA	Ian		Intra cellular boron distribution evaluation by neutron autoradiography	Pa B3 01
POSTUMA	Ian		Use of EpiskinTM to evaluate BNCT radiation damage to healthy tissue	Pa B3 02
PRAENA	Javier		Results of the measurements of the 33S(n,α)30Si cross-section at CERN and ILL: application to NCT	PS2 P 08
PROTTI	Nicoletta		Preliminary performance studies of a CZT photon detector using a highly thermalized neutron beam.	PS1 B 04
PROTTI	Nicoletta		High performance 3D CZT spectro-imager for BNCT-SPECT: preliminary characterization.	PS1 B 05
PROTTI	Nicoletta		Prompt gamma tomography for BNCT-SPECT: a feasibility study using a small animal phantom.	Pa B3 03
PROVENZANO	Lucas		Exploring neutron autoradiography and alpha spectrometry techniques for boron measurements in bone.	Pa B2 05
PROVENZANO	Lucas		Computational assessment of BNCT neutron beams using radiobiological models	Pa P3 05
QUAH	Daniel Song Chiek		Boron Neutron Capture Therapy for High-Grade Gliomas – Consolidating Published Evidence in One Place	Pa Cl2 04
QUAH	Daniel Song Chiek		First Patient from Singapore to Receive Boron Neutron Capture Therapy - Challenges Met and Lessons Learnt	Pa Cl2 05
QUAH	Daniel Song Chiek		Dosimetric Comparison of Boron Neutron Capture Therapy, Proton Therapy and IG-IMRT for Recurrent Anaplastic Meningioma	Pa Cl2 06
SAKURAI	Yoshinori		Improvement of gamma-ray telescope system for BNCT at Kyoto University Reactor	Pa P4 01
SAKURAI	Yoshinori		The history of the development of reactor-based neutron source for BNCT	Pl P1 02
SANADA	Yu		Disruption of Hif-1α enhances the sensitivity to BNCT in murine squamous cell carcinoma	PS1 R 08
SANTA CRUZ	Gustavo	Alberto	DYNAMIC INFRARED IMAGING FOR BIOLOGICAL AND PRECLINICAL STUDIES IN BNCT	Pa R3 05
SANTOS	Daniel		Accelerator Based Neutron Capture Therapies in France	Pa P5 02
SARTA FUENTES	Jose Antonio		CURRENT STATUS OF NEUTRON CAPTURE THERAPY IN COLOMBIA	PS2 M 01
SATO	Michitaka		Development of real-time neutron detector for beam quality discrimination measurement using LiCAF scintillator and neutron moderator	Pa P3 01
SAUERWEIN	Wolfgang	A.G.	Reporting BNCT: A new approach towards an international standard	Pa Cl2 02
SEKI	Ryoichi		A Simplification in BNCT Treatment Planning: Two-component Treatment of Inhomogeneous, Multi-component Dose Distributions, Based on Dose-Fraction Regularity	Pa P4 05
SEO	Hyo Jung		Development of the accelerator based Boron Neutron Capture Therapy system for cancer treatment within 1-hour therapeutic time	Pa P1 04
SEO	Hyo Jung		Development of Proton Linear Accelerator based Boron Neutron Capture Therapy System in Republic of Korea	Pa M1 02
SHIBATA	Saki		Design of collimator for T/N-SPECT for BNCT	PS1 B 01
SHIRAISHI	Sadaaki		Development of remote-changeable Bonner sphere spectrometer	Pa M1 07

Author Index

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
SHIRAKAWA	MAKOTO		Preparation methods of liposome which encapsulated boron compound at high concentration and efficiency.	PS2 Ch 04
SHU	Diyun		Cherenkov radiation and its application in Boron Neutron Capture Therapy	Pa M1 03
SKALYGA	Vadim		Status of BNCT Neutron Generator Development at the IAP RAS	Pa P4 07
STEPHAN	Chady		Single Cell ICP-MS: Quantification of Metal Content in Individual Cells - An Insight into Cancer Treatment	Pa B1 05
SUJUNG	Chen		Radiolabeling and In Vivo Image Evaluation of Boron containing neuropeptide(NPY) analogue in breast cancer	PS1 R 07
SUZUKI	Minoru		Boron neutron capture therapy for malignant pleural mesothelioma: A case report	Pa Cl2 03
SYCHEVA	Tatiana		Optimization of the beam shaping assembly and local protection of the accelerator source of epithermal neutrons	PS1 P 04
TAKADA	Masashi		Development of Real-Time BNCT Neutron Beam Monitor Using Thin Silicon Sensor	Pa P3 08
TAKADA	Kenta		Computational evaluation of dose distribution including radiation exposure to ambient organs for BNCT treatment combined with X-ray therapy or proton beam therapy	Pa P5 01
TAKAI	Yoshihiro		Accelerator-based BNCT at Southern TOHOKU general hospital--The world's first BNCT Hospital- Roadmap to Pharmaceutical Affairs Regulatory Approval	Pl Cl1 01
TAKATA	Takushi		Patient-Position Monitoring System for BNCT Irradiation	PS1 P 17
TAKEUCHI	Akihiko		Impact of inter-observer variability for mucosal delineation on the dosimetry of boron neutron capture therapy for head and neck cancer	PS2 Cl 02
TAMAKI	Shingo		Development and experimental verification of a liquid moderator based neutron spectrometer	Pa P1 05
TANAKA	Kenichi		Investigation of 124Sb-Be neutron source for BNCT.	PS1 P 10
TANAKA	Kenichi		Investigation of beam component monitor for BNCT using gel detector	PS1 P 11
TANAKA	Hiroki		Development of thermal neutron irradiation port for cells and small animals using 20MeV cyclotron and beryllium target	Pl P1 01
TASKAEV	Sergey		Accelerator Neutron Source for in-vitro and in-vivo BNCT studies	Pa P1 01
TASKAEV	Sergey		In Situ Observations of Blistering of a Metal Irradiated with 2-MeV Protons	Pa P1 02
TONG	Jianfei		Recent Development of BSA in D-BNCT	Pa Ph6 01
TORRES-SANCHEZ	Pablo		On the upper limit for the energy of epithermal neutrons for BNCT	Pa P3 04
TRIVILLIN	Veronica	A	BORON NEUTRON CAPTURE THERAPY (BNCT) COMBINED WITH BCG AS IMMUNOTHERAPY IN AN ECTOPIC COLON CONCER MODEL: LOCAL AND ABSCOPAL EFFECTS	Pa R3 03
TSAI	Wen-Chyi		Measurement of gamma-ray dose and neutron activation in BNCT beams using TLD-200	PS2 P 03
TSUCHIDA	Kazuki		Compact Accelerator-Driven BNCT System Used Sealed Lithium Target	Pa Ph6 04
TYMINSKA	Katarzyna		BNCT RESEARCH FACILITY AT MARIA REACTOR (NCBJ, POLAND) – NUMERICAL MODELS AND FIRST MEASUREMENTS	Pa P2 06
UCHIDA	Ryohei		Radiation quality dependence of polymer gel dosimeters in therapeutic neutron irradiation field	Pa P2 10
VALERO	Matias		PGNAA facility at RA-3: numerical approach towards first measurements of biological samples for BNCT	PS1 B 06
VOHRADSKY	James		Evaluation of silicon based microdosimetry for boron neutron capture therapy Quality Assurance using fast neutron beams	Pa P1 08
WANG	Ta-Wei		Development of boron-loaded Microbubbles for Focused Ultrasound Triggered Brain Tumor Drug Delivery	PS2 Ch 05
WANG	Ling-Wei		Boron neutron capture therapy (BNCT) combined with image-guided intensity modulated radiotherapy (IG-IMRT) for treatment of recurrent Head & Neck cancer	Pl Cl1 04

Last_name	First_name	Middle_name	Submission Title	Presentaion Code
WINKLER	Alexander		A virtual neutron anti-scatter grid for future Cd(Zn)Te based BNCT-SPECT systems	Pa B1 01
WU	Yuan-Hung		Treatment outcome of recurrent meningioma, diffuse intrinsic pontine glioma, recurrent extracranial rhabdomyosarcoma, and recurrent inverted papilloma	Pl Cl2 02
XIAOPING	Zhou		Neutron Photon irradiation damage analysis of human tissue for BNCT based on Geant4	PS2 P 13
YANAGAWA	Masashi		Pilot study of Gadolinium Accumulation in Tumour with Intra-arterial Administration of Gadoteridol-Entrapped Water-in-Oil-in-Water Emulsion in VX-2 Rabbit Hepatic Cancer Model for Neutron Capture Therapy	PS2 M 03
YANAGIE	Hironobu		Preparation of Water-in-Oil-in-Water Emulsion as Drug Delivery System Using Mixing Medical Device for Neutron Capture Therapy	Pa M1 06
YAO	Ying		Enhanced tumor-targeted delivery of p-boronophenylalanine using fructose-functionalized polymers for boron neutron capture therapy	Pa Ch1 04
YASUI	SEIJI		Defining the molecular characteristics of boron compounds proposes the concept of precision medicine in BNCT field	Pa Cl1 04
YOE	Shih-De		Evaluation of Multi-field Technique Applied to Boron Neutron Capture Therapy for Brain Tumors	Pa P4 06
YOSHIDA	Fumiyo		Difference in BPA uptake between glioma stem cells and their cancerous cells	PS1 Ch 02
YOSHIHASHI	Sachiko		Accelerator based BNCT system in Nagoya University -Development of a sealed lithium target-	PS2 P 10
ZABORONOK	Alexander		Hybrid gold and boron nanoparticles for treatment and boron dose estimation in boron neutron capture therapy for malignant glioma	Pa R1 01
ZAILANI	Rosilatul		Current Status of Research and Development Boron Neutron Capture Therapy in Indonesia	Pa Ph6 05
ZHANG	Xudong		Strategies for consistently assessing the response of radiochromic film using flatbed scanners	Pa M1 04
ZHANG	Wei		The Physical Design of a Modular Neutron Source Assembly for BNCT	PS2 P 16
ZHANG	Zi-zhu		Biodistribution studies of boronophenylalanine-fructose complex in different types of skin melanoma	Pl Cl1 03

理未易察

Truth is not easy to be understood