



16TH INTERNATIONAL CONGRESS

NEUTRON CAPTURE THERAPY

JUNE 14–19, 2014

HELSINKI, FINLAND

[HTTP://ICNCT16.ORG/](http://icnct16.org/)



FEDERATION OF FINNISH LEARNED SOCIETIES



Cancer Society of Finland



Time Table

16th
ICNCT
Conference

	Saturday June 14th	Sunday June 15th	Monday June 16th
8:00			
9:00		9:15–9:45 Opening Ceremony	9:00–10:30(40) Parallel Sessions: Physics 1 Biology 1 Chemistry 1
10:00	9:30–12:15 Training Course: Tumor Basics, Radiobiology and Microdosimetry	9:45–10:30 Hatanaka Lecture	
		10:30–11:00 Coffee Break	10:30–11:00 Coffee Break
11:00	Helsinki University Central Hospital Department of Oncology Lecture Hall	11:00–12:30 Plenary Clinical 1	11:00–12:40 Plenary Biology I
12:00	12:15–12:45 Lunch		
13:00	12:45–14:00 Training Course: Tumor Basics, Radiobiology and Microdosimetry	12:30–13:30 Lunch	12:40–13:40 Lunch
14:00		13:30–14:30 Special Lecture	13:40–14:40 Plenary Chemistry 1
		14:00–19:00 Registration	
15:00	15:00– 16:00 Executive Board Meeting	14:30–16:10 Plenary Clinical 2	14:40–16:40 Coffee Break & Poster Viewing 1
16:00	16:00–17:00 Board of Councillors Meeting	16:10–16:40 Coffee Break	
17:00		16:40–18:15 Plenary Clinical 3	16:40–18:20 Parallel Sessions: Physics 2 Boron Imaging 1 Chemistry 2
18:00	18:00– Welcome Reception		
19:00		18:30–19:45 IAEA TECDOC workshop	18:30–19:45 ISNCT workgroup meetings

Tuesday June 17th	Wednesday June 18th	Thursday June 19th
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		8:00 – 8:45 Executive Board Meeting	8:00
		8:45 – 9:15 Board of Councilors Meeting	
9:00–11:00 Parallel Sessions: Physics 3 Physics 4 Boron Imaging 2	9:00–10:00 Plenary Biology 2	9:30–10:30 Parallel Sessions: Physics 6 Chemistry 3	9:00
	10:00–11:00 Plenary Physics 1	10:30–11:00 Coffee Break	10:00
11:00–11:30 Coffee Break	11:00–11:30 Coffee Break	11:00–12:00 Plenary Physics 2	11:00
11:30–12:30 Invited Lecture PET-imaging	11:30–12:30 Invited Lecture Clinical	12:00–12:45 Round Table Discussion and Closing	12:00
12:30– 18:30	12:30–13:30 Lunch	12:45–13:45 Lunch	13:00
Optional Boat Excursion Tour to Södeskär lighthouse	13:30–15:10 Parallel Sessions: Physics 5 Clinical 1 Biology 2	14:00–17 Optional Tour: FiR 1, Otaniemi	14:00
	15:10–17:10 Coffee Break & Poster Viewing 2	FiR 1 excursion and presentation seminar on European Spallation Source (ESS)	15:00
	17:10–18:00 ISNCT General Assembly		16:00
			17:00
			18:00
19:00– Reception at the Helsinki City Hall	19:00– Official Banquet		19:00

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Syöpä ja pahoinvointi



Paremmän elämän puolesta

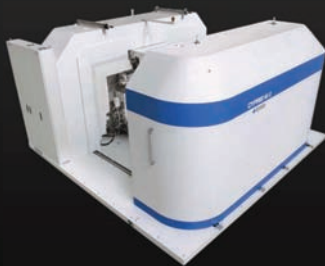
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Unigrafia Oy
Helsinki 2014





Advancing
cancer care

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Tenboron Oy
Viikinkaari 6
00790 Helsinki
Finland

Welcome

Dear Colleagues



The 16th International Congress on Neutron Capture Therapy (NCT) will take place for the first time in Fenno-Scandinavia, in Helsinki, Finland from Saturday June 14 through Thursday June 19, the week of midsummer.

The conference will offer the opportunity to present the latest clinical results in the treatment of cancer using Boron Neutron Capture Therapy (BNCT) and to learn of the latest techniques and clinical applications of the leaders in the various disciplines pertinent to BNCT. Key topical areas of the scientific program will include the development of hospital-deployable accelerator-based neutron sources and next-generation boron targeting agents for BNCT, as well as highlights of the latest basic biological, biophysical and clinical research. This meeting will be a perfect venue to meet and interact with multi-disciplinary experts in BNCT, to develop new professional connections, and to contribute to ongoing advancements on the frontier of BNCT. During the conference, meetings of the governing bodies of the International Society for Neutron Capture Therapy (ISNCT), a General Assembly, and meetings of many specialized technical working groups will be conducted as well, offering additional opportunities to become involved in the many scientific aspects of this important field of medical research. Finally, a social program targeting Helsinki city specialties and Nordic design and culture in the attractive natural environment of the Finnish archipelago at midsummer, with its pleasant and seemingly endless days, will make this meeting even more special.

Thus it is my great pleasure to invite colleagues in all professions related to BNCT to the 16th ICNCT International Congress. The meeting will be a key milestone in the further development of BNCT as a single-session therapy in radiation oncology.

With best regards we cordially welcome you and your team in Helsinki.

Leena Kankaanranta

MD Oncologist

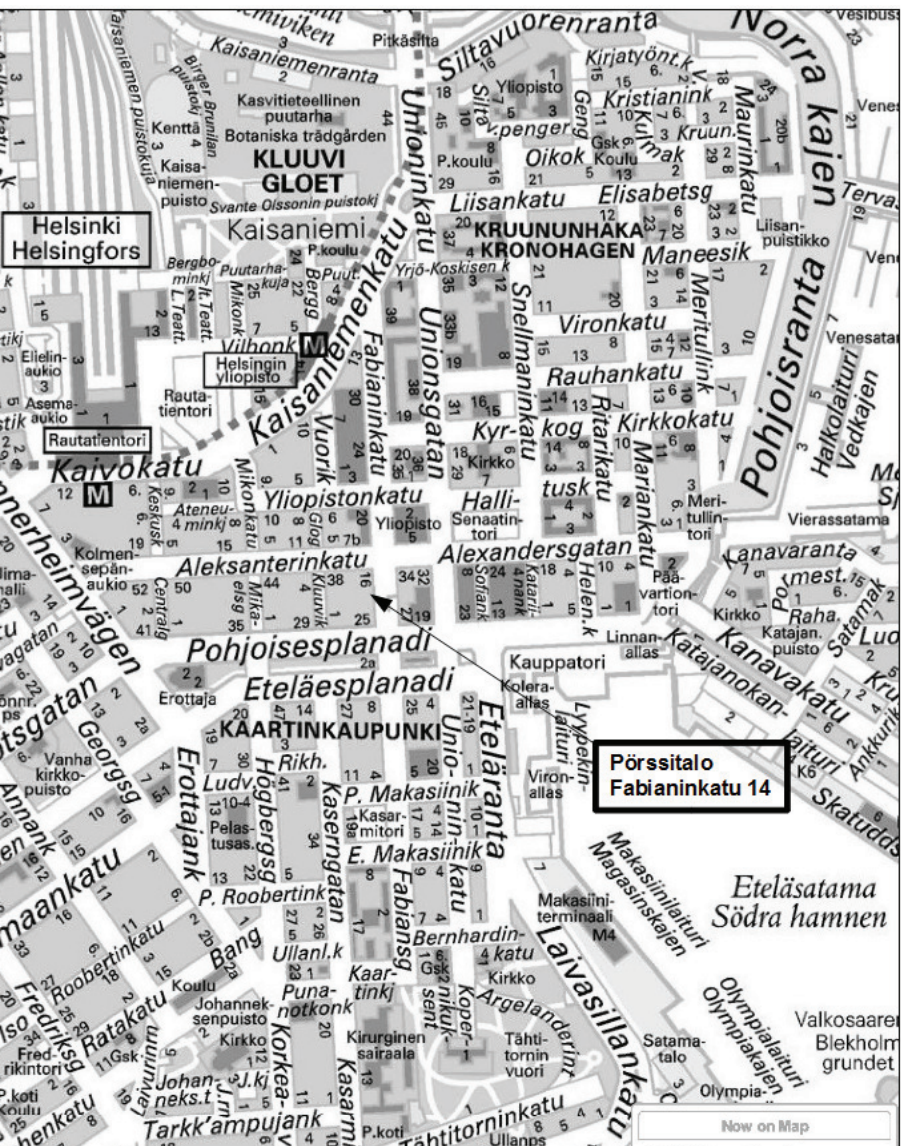
President of the 16th ICNCT meeting

President of the International Society for Neutron Capture Therapy

Congress venue

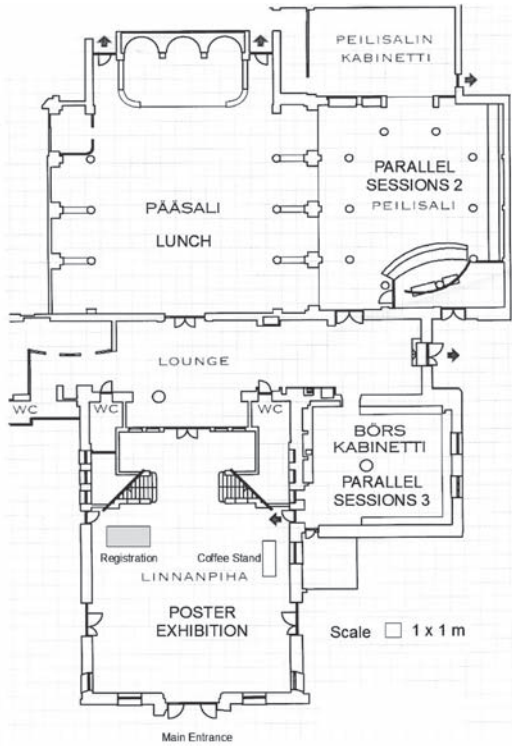
The venue of the 16th ICNCT is **Pörsstalo** (the former venue of the Finnish Stock Exchange), located in the city center of Helsinki.

Address: Fabianinkatu 14, 00100 Helsinki, Finland

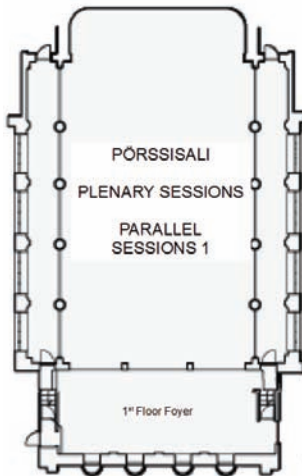


Floor Maps

Ground Floor



1st Floor



16th International Congress on Neutron Capture therapy Congress Committees

Local Organizing Committee

Leena Kankaanranta, President
Iiro Auterinen, Vice President
Hanna Koivunoro, Secretary General
Petteri Välimäki
Vappu Reijonen
Tiina Seppälä
Martti Kulvik
Mika Kortnesniemi
Jouni Uusi-Simola
Eero Hippeläinen (Technical assistant)

Local Scientific Committee Clinical Matters

Heikki Joensuu
Leena Kankaanranta
Antti Mäkitie
Aaro Haapaniemi
Mauri Kouri
Matti Seppälä
Juha Jääskeläinen

Radiobiology

Martti Kulvik
Iiro Auterinen
Päivi Arponen-Esteves

Chemistry and Pharmacology

Filip Ekholm
Vappu Reijonen

Medical Physics

Sauli Savolainen
Antti Kosunen
Hanna Koivunoro
Tiina Seppälä
Jouni Uusi-Simola

Neutron Sources

Iiro Auterinen
Petri Kotiluoto
Hanna Koivunoro

Boron Determination and Imaging

Hannu Revitzer
Marjut Timonen
Iiro Auterinen

Scientific Committee

Saverio Altieri
Päivi Arponen-Esteves
Iiro Auterinen
Rolf Barth
William Bauer
Silva Bortolussi
Maria Dagrosa
Allah Detta
Filip Ekholm
Detlef Gabel
Grazia Gambarini
Sara González
Aaro Haapaniemi
John Hopewell
Yen-Wan Liu Hsueh
Satish Jalisatgi
Stead Kiger
Yuko Kinashi
Mitsunori Kiriata
Tooru Kobayashi
Hanna Koivunoro
Petri Kotiluoto
Mauri Kouri
Andres Kreiner
Martti Kulvik
Hiroaki Kumada
Yuan-Hao Liu
Shin-ichiro Masunaga
Daniel M Minsky
Antti Mäkitie
Kei Nakai
Hiroyuki Nakamura
Dave Nigg
Ben Phoenix
Nicoletta Protti

Laura Roveda
Yoshinori Sakurai
Gustavo Santa Cruz
Sauli Savolainen
Mandy Schwint
Christian Schütz
Marko Seppänen
Hiroki Tanaka
Sergey Taskaev
Marjut Timonen
Verónica Andrea Trivillin
Jouni Uusi-Simola
Ling-Wei Wang
Tetsuya Yamamoto
Alba Zanini

Award Recipients

Hatanaka Award

Shin-Ichi Miyatake

Fairchild Awards

Esteban Fabián Boggio
Madleen Busse
Chih-Ting Chang
Rubén Fariás and Marcela Garabilino
Gen Futamura
Mario Alberto Gadan
Andrea Monti Hughes
Masanobu Manabe
Ian Postuma
Ricardo Ramos
Shingo Tamaki
Sheng Yan

ISNCT – International Society for Neutron Capture Therapy Executive Board

Leena Kankaanranta (President)

Satish Jalistagi (President-Elect)

Akira Matsumura (Immediate Past President)

Dave Nigg (Secretary-Treasurer, 2010-2016)

Silva Bortolussi (Elected Member, 2012-2016)

Stuart Green (Elected Member, 2010-2014)

Andres Kreiner (Elected Member, 2010-2014)

Iiro Auterinen (Elected Member, 2010-2014)

Tetsuya Yamamoto (Elected Member, 2010-2014)

Board of Councilors

End of term 2014

Tooru Kobayashi

Kent Riley

Detlef Gabel

Luigi Panza

Koji Ono

John Hopewell

Teruyoshi Kageji

Garth Cruikshank

Tetsuya Yamamoto

Gustavo Santa Cruz

End of term 2016

Junichi Hiratsuka

Ling-Wei Wang

Amanda Schwint

Alejandra Daggrossa

Hiroyuki Nakamura

Luca Menichetti

Silva Bortolussi

Yuan-Hao Liu

Hanna Koivunoro

Stead Kiger

End of term 2018

Akira Matsumura

Shin-Ichi Miyatake

Andrea Wittig

Shin-Ichiro Masunaga

Veronica Trevillin

Mitsunori Kirihata

Satish Jalistagi

Hiroaki Kumada

Iiro Auterinen

Saverio Altieri

The History of ICNCT

1st	Cambridge, USA	Brownell and Fairchild	1983 12–14 October
2nd	Tokyo, Japan	Hiroshi Hatanaka	1985, 18–20 October
3rd	Bremen, Germany	Detlef Gabel	1988, 31 May-3 June
4th	Sydney, Australia	Barry J Allen	1990, 4-7 December
5th	Columbus, USA	Albert J Soloway	1992, 14–17 September
6th	Kobe, Japan	Yutaka Mishima	1994, 31 October-4 November
7th	Zurich, Switzerland	Borje Larsson	1996, 4-7 September
8th	La Jolla, USA	Frederick Hawthorne	1998, 13–18 September
9th	Osaka, Japan	Keiji Kanda	2000, 2–6 October
10th	Essen, Germany	Wolfgang Sauerwein	2002, 8–13 September
11th	Boston, USA	Robert Zamenhof	2004, 11–15 October
12th	Takamatsu, Japan	Yoshinobu Nakagawa	2006, 9–13 October
13th	Florence, Italy	Aris Zonta	2008, 2–7 November
14th	Buenos Aires, Argentina	Sara J Liberman	2010, 25–29 October
15th	Tsukuba, Japan	Akira Matsumura	2012, 10–14 Septembcr
16th	Helsinki, Finland	Leena Kankaanranta	2014, 14–19 June
17th	Missouri, USA	Satish Jalistagi	2016

Congress Information

Congress Registration Desk and Secretariat

Place:	Ground floor, Pörssitalo
Office hours:	Saturday, June 14th: 14:00 – 19:00
Sunday, June 15th:	8:45 - 18.30
Monday, June 16th:	8:45 - 18.30
Tuesday, June 17th:	8:45 - 13.30
Wednesday, June 18th:	8:45 - 18.00
Thursday, June 19th:	9:00- 14.00
Phone:	+358 (0) 9 434 2590

Internet Service:	WiFi is available in Pörssitalo. Ask at the Registration desk
Official Language	English

Social Program

Saturday, June 14th

Welcome Reception

Venue: Restaurant, Pörssitalo

Time: 18:00-

Tuesday, June 17th

Reception by the City of Helsinki

Venue: Helsinki City Hall

Time: 19:00-

Wednesday, June 18th

Official Banquet

Time: 19:00-

Excursions

Boat cruise to Söderskär light house

Tour time: Tuesday June 17th, 14:00-18

Meeting point: Main entrance hall of the congress center (Pörssitalo)

Söderskär (*meaning southern rock*), formed by rough cliffs and rocky islands, lies in the outer archipelago of Porvoo against the open sea, 2 hours boat trip away from the Helsinki market place. The uniqueness of Söderskär lies within the impressive milieu, but of course also the lighthouse itself.

The lighthouse represents the mysticism of adventure, previous times and extreme circumstances. In their imagination visitors can walk in the footsteps of the past lighthouse workers and pilots. The peaceful milieu and the sea create circumstances, in which it's easy to shake off the dust of the city and give room to your own thoughts and imagination. Söderskär calls visitors to enjoy peace and creative atmosphere in the middle of the sea!

Söderskär has inspired also the imagination of many Finnish artists, **Tove Jansson**, the author of Moomin stories being one of the most famous ones. The lighthouse from the book *Moominpappa and the Sea* is said to be Söderskär. We'll take a cruise boat from the Helsinki market place, which locates next to the conference venue Pörssitalo. Lunch will be served on the cruise boat (included in the fee). We'll return before start of Reception at the Helsinki City Hall (located also next to the boat harbor).

FiR 1 excursion and European Spallation Source presentation seminar

Tour time: Thursday June 19th, 14:00-17

Meeting point: Main entrance hall of the congress center (Pörssitalo)

SCHEDULE

- 14:00 Busses leave from Pörssitalo, the venue of ICNCT-16
- 14:20 Arriving at Otakaari 3 A, Otaniemi, campus of the Aalto University and VTT Technical Research Centre of Finland
- 14:30 Main lecture Lecture Hall F239a, Otakaari 3
Short introduction to FiR 1 nuclear research reactor and visiting procedures, **Iiro Auterinen**, VTT
- 14:45 Visiting groups 1-4 (max 50 persons) leave for the reactor
- 14:50 General introduction to the European Spallation Source (ESS)-project and the instruments, **Esko Oksanen**, ESS
- 15:15 Visiting groups 1-4 return from the reactor and groups 5 – 8 (max 50 persons) leave for the reactor
- 15:20 General introduction to the European Spallation Source (ESS)-project and the instruments, **Esko Oksanen**, ESS
- 15:45 Visiting groups groups 5 – 8 (48 persons) return from the reactor
Refreshments
- 16:00 ESS- accelerator and target station – possibilities for BNCT research, **Riccardo Bevilacqua**, ESS
- 16:15 Discussion on the possibilities ESS offers for BNCT research
- 16:45 Busses return to Helsinki

Instructions for Speakers

For Oral Session Speakers

- The plenary lectures (15 minutes or 20 minutes) highlight some major research questions relevant to all of us.
- The parallel sessions reflect the multidisciplinary nature of NCT research. The parallel session presentations (15 minutes) will provide unique opportunities for updates on each specialty.
- Every presentation will be followed by 5 minutes of discussion.
- The preferred presentation format is PowerPoint; alternatively pdf can be used. Please save your PowerPoint with embedded font.
- Windows (Windows 7 professional, Office 2010) is the only operating system available for the presentations.
- Use of own PC or Macintosh for presenting is not possible.
- Uploading of the presentations will be provided through the conference website. These are checked for compliance with the presentation computers by the organizer.
- Alternatively and for late changes presentations can be brought on a CD-Rom or USB memory device to the Speakers Center.

For Poster Session Presenters

- The mounting space available for your poster is 95 cm x 160 cm (width x height). The posters are advised to be printed on a paper approximately of A0 size (84.1 cm x 118.9 cm).
- Posters will be mounted using pins that will be provided on the spot.
- Uploading of the pdf-prints of the posters will be provided through the conference website for sharing with the conference participants.

There are two poster sessions scheduled in program

- The posters for the first session scheduled on Monday, June 16th, should be mounted starting from the registration time and removed after the poster session ends.
- The posters for the second poster session scheduled on Wednesday, June 18th, should be mounted beginning from the Tuesday morning and removed by Thursday, June 19th.
- Poster authors should be prepared to give a one minute "elevator pitch" (http://en.wikipedia.org/wiki/Elevator_pitch) of their poster. Poster session chairmen will select those who get this opportunity to present their poster through the loudspeaker system.

Program

Saturday June 14th

9:30-14:00 Training Course – Tumour Basics, Radiobiology and Microdosimetry

Location

HUS – Helsinki University Central Hospital

Department of Oncology Lecture Hall

Haartmaninkatu 4, 00290 Helsinki

9:30-9:45 Welcome and Introduction of Lecturers

Leena Kankaanranta & Iiro Auterinen

9:45-10:30 Cancer Basics: Invasion, Metastasis and Tumor Angiogenesis

Rolf Barth, Professor of Pathology, The Ohio State University, USA

10:30-11:15 Basics of radiobiology

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

11:15-11:30 Break

11:30-12:15 The influence of microdistribution of B-compound on the reaction of a cell or tissue

Koji Ono, Professor, Radiation Oncology, Kyoto University

12:15-12:45 Lunch

12:45-13:15 *Basics of the tumour control probability in radiotherapy*

Sara Gonzalez, National Atomic Energy Commission , Argentina

13:15-14:00 *Radiobiology studies and proportional counter microdosimetry and the their role in BNCT*

Stuart Green, Director of Medical Physics, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham, UK

14.00-14.30 *Possibility for a tour in the HUCH Cancer Clinic*

14:00-19:00 *Registration*

Pörssitalo, Linnanpiha

18:00-20:00 *Welcome Reception*

Pörssitalo, Pääsali

Sunday June 15th

9:15-9:45 Opening

Pörssisali

9.45-10.30 Hatanaka Lecture

Session Chair: **Leena Kankaanranta**

- **Shin-Ichi Miyatake**, Osaka Medical College, Osaka, Japan: *Development of BNCT in 12 years at Osaka Medical College*

10:30-11:00 Coffee

11:00-12:30 Plenary Clinical 1 (PI C1) Pörssisali

Session Chairs: Koji Ono & Leena Kankaanranta

- 11:00-11:25 **Itsuro Kato**, Department of Oral and Maxillofacial Surgery II, Osaka University, Graduate School of Dentistry, Osaka, Japan: *Boron Neutron Capture Therapy in Patients with Recurrent Head and Neck Cancers Who Have No Other Treatment Options*
- 11:25-11:50 **Ling-Wei Wang**, Taipei Veterans General Hospital, Taiwan: *Fractionated BNCT for locally recurrent head and neck cancer at THOR: an update of treatment results*
- 11:50-12:10 **Hironobu Yanagie**, Department of Innovative Cancer Therapeutics, Meiji Pharmaceutical University, Japan: *Clinical Experiences of Boron Neutron Capture Therapy to Recurred Rectal Cancers*
- 12:10-12:30 **Leena Kankaanranta**, Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland: *Building on the Finnish BNCT experience - Visions into Future*

12:35-13:30 Lunch

13:30-14:15 Special

Pörssisali

Session Chairs: **Stead Kiger & Maria Herrera**

- 13:30-13:50 **Yoshio Imahori**, Cancer Intelligence Care Systems, Inc., Tokyo, Japan: *Accelerator-based epithermal neutron source for BNCT using thin-layer solid-Lithium target*
- 13:50-14:10 **Kazuyo Igawa**, Southern TOHOKU General Hospital, Fukushima, Japan: *Accelerator-based Boron Neutron Capture Therapy in Southern TOHOKU General Hospital*
- 14:10-14:30 **Akira Matsumura**, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan: *i-BNCT project. An accelerator based in-hospital BNCT*

14:30-15:45 Plenary Clinical 2 (PI C2)

Pörssisali

Session Chair: **Martti Kulvik**

- 14:30-14:55 **Aaro Haapaniemi**, Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Central Hospital and University of Helsinki, Finland: *Boron Neutron Capture Therapy (BNCT) in the Management of Recurrent Laryngeal Cancer*
- 14:55-15:20 **Junichi Hiratsuka**, Department of Radiation Oncology, Kawasaki Medical School, Kurashiki, Japan: *Clinical results of BNCT for Head and Neck melanoma*
- 15:20-15:45 **Teruyoshi Kageji**, Department of Neurosurgery, The University of Tokushima, Tokushima, Japan: *Radiation-induced meningiomas after BNCT in patients with malignant glioma*
- 15:45-16:10 **Song Chiek Quah**, National Cancer Centre, Singapore, 11 Hospital Drive, Singapore: *Boron Neutron Capture Therapy for Locally Recurrent Head and Neck Cancer –A Review of Literature and A Comparison Against Systemic Therapy*

16:10-16:40 Coffee

16:40-18:15 Plenary Clinical 3 (PI C3)

Pörssisali

Session Chairs: **Akira Matsumura** & **Garth Cruickshank**

- 16:40-17:05 **Desire Ngoga**, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham & School of Cancer Sciences, University of Birmingham: *Glioma heterogeneity and the L-Amino acid transporter-1 (LAT1): A first step to stratified BPA-based BNCT?*
- 17:05-17:30 **Mario Gadan**, Comisión Nacional de Energía Atómica, Argentina: *Application of BNCT to the treatment of HER2+ breast cancer recurrences: research and developments in CNEA*
- 17:30-17:55 **Garth Cruickshank**, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham & School of Cancer Sciences, University of Birmingham: *Pharmacokinetic analysis of Carotid BPA-Mannitol delivery in Human GBM, indicates three compartment tumour uptake kinetics enhanced by specific LAT activity in the Brain Around Tumour after resection*
- 17:55-18:15 **Hanna Koivunoro**, HUS Helsinki Medical Imaging Center, Helsinki University Central Hospital: *Biokinetic analysis of tissue 10B concentrations of glioma patients treated with BNCT in Finland*

18:30-19:45 IAEA TECDOC workshop

Monday June 16th

9:00-10:40 *Parallel Physics 1 (Pa P1)*

Peilisali

Session Chairs: **Tooru Kobayashi** & **Andres J. Kreiner**

- 9:00-9:20 **Andres J. Kreiner**, Comisión Nacional de Energía Atómica (CNEA) - Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) - 5Escuela de Ciencia y Tecnología (UNSAM), San Martín, Buenos Aires, Argentina: *Present Status of Accelerator-Based BNCT*
- 9:20-9:40 **Tooru Kobayashi**, Kyoto University Research Reactor Institute, Osaka, Japan: *Future of Accelerator Based BNCT Neutron Irradiation System using Liquid Lithium Target for ${}^7\text{Li}(p,n){}^7\text{Be}$ Near Threshold Reactions*
- 9:40-10:00 **Masakazu Yoshioka**, KEK, Accelerator Research Organization, Japan: *Construction of Accelerator-based BNCT facility at Ibaraki Neutron Medical Research Center*
- 10:00-10:20 **Andrea Pisent**, MUNES project, Italy: *MUNES project: an intense Multidisciplinary Neutron Source for BNCT based on a high intensity RFQ accelerator*
- 10:20-10:40 **María S. Herrera**, Comisión Nacional de Energía Atómica (CNEA) - Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina: *Analyzing the performance of accelerators in BNCT: evaluation of the therapeutic potential of the proposed facility and its comparison with global benchmark clinical beams*

MON

9:00-10:30 Parallel Biology 1 (Pa B1)

Pörssisali

Session Chairs: **Verónica A Trivillin** & **Shin-Ichiro Masunaga**

- 9:00-9:20 **Rolf Barth**, Department of Pathology, The Ohio State University, Columbus, Ohio, USA: *Evaluation of Caboranyl Thymidine Analogues as Potential Delivery Agents for Boron Neutron Capture Therapy*
- 9:20-9:40 **Melinda Bartok**, School of Engineering and Science, Jacobs University Bremen, Germany: *Dodecaborate clusters forms stable pores in lipid membranes*
- 9:40-10:00 **Andrea Monti Hughes**, National Atomic Energy Commission (CNEA), Argentina: *Histamine reduces BNCT induced mucositis in precancerous tissue without affecting BPA biodistribution or long term inhibition of tumor development*
- 10:00-10:20 **Katia Alikaniotis**, Università di Torino, Italy: *Combined effect of e-LinAc high-energy radiotherapy treatment and BNCT on human cell lines*
- 10:20-10:40 **Cinzia Ferrari**, Department of Clinico-Surgical Sciences, Experimental Surgery Laboratory, University of Pavia, Italy: *Comparative Study of the Radiobiological Effects Induced on Adherent vs Suspended Cells by BNCT, Neutrons and Gamma Rays Treatments*

9:00-10:30 Parallel Chemistry 1 (Pa Ch1)

Börs-kabinetti

Session Chair: **Luigi Panza**

- 9:00-9:20 **Po-Shen Pan**, Tamkang University, Taiwan: *Direct Synthesis of Boron-containing Ugi Analogues and their Biological Evaluations*
- 9:20-9:40 **Hiroyuki Nakamura**, Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo - Chemical Resources Laboratory, Tokyo Institute of Technology, Yoko-

hama, Japan: *Development of Albumin-bound closo-Dodecaborate and its Promising Boron Delivery Efficacy to Tumor*

- 9:40-10:00 **Madleen Busse**, School of Chemistry, The University of Sydney, Sydney, Australia: *Gadolinium Neutron Capture Therapy Agents Targeting Mitochondria*
- 10:00-10:20 **Novriana Dewi**, Dept of Nuclear Engineering & Management, The University of Tokyo, Japan: *In vivo evaluation of Gd-DTPA-incorporated calcium phosphate nanoparticles for neutron capture therapy agent*

10:30-11:00 *Coffee*

11:00-12:40 **Plenary Biology 1 (Pl B1)**

Pörssisali

Session Chairs: **Dave Nigg** & **Sauli Savolainen**

- 11:00-11:25 **Rolf Barth**, Department of Pathology, The Ohio State University, Columbus, Ohio, USA: *From Translation BNCT Studies in Animals to Clinical Trials*
- 11:25-11:50 **Verónica A. Trivillin**, Comisión Nacional de Energía Atómica (CNEA) - CONICET, Argentina: *BNCT in an experimental model of lung metastases in BDIX rats*
- 11:50-12:15 **Tooru Andoh**, Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University, Japan: *Boron neutron capture therapy as new treatment for clear cell sarcoma: Trial on a lung metastasis model of clear cell sarcoma*
- 12:15-12:40 **Gen Futamura**, Department of Neurosurgery, Osaka Medical College, Japan: *Examination of the usefulness as the new boron compound of ACBC-BSH*

12:40-13:40 *Lunch*

13:40-14:40 Plenary Chemistry 1 (PI Ch1)

Pörssisali

Session Chair: **Detlef Gabel**

- 13:40-14:00 **Detlef Gabel**, School of Engineering and Science, Jacobs University Bremen, Germany: *Boron clusters as boron carriers for BNCT: Possibilities and problems*
- 14:00-14:20 **Madleen Busse**, School of Chemistry, The University of Sydney, Australia: *High Mitochondrial Accumulation of New Gadolinium Agents Within Tumor Cells For Binary Cancer Therapies*
- 14:20-14:40 **Juhani Saarinen**, Glykos Finland Oy and Tenboron Oy, Helsinki, Finland: *Development of novel boron carriers for BNCT*

14:40 Coffee

Linnanpiha

14:40-16:40 Posters 1, Clinical (PS1 C)

Linnanpiha

01 *An improved electronic collection of BNCT literature*, **Wolfgang Sauerwein**, University Duisburg-Essen, University Hospital Essen, Germany

02 *A Strategy to Succeed BNCT for the Practical Situation*, **Tooru Kobayashi**, Kyoto University Research Reactor Institute, Japan

03 *Overview of the re-initiation of BNCT clinical studies at the University of Tsukuba*, **Teruhito Aihara**, Proton Medical Research Centre, University of Tsukuba, Japan

04 *Clinical irradiation bed system with 3D-optimization algorithm for BNCT*, **Tsuyako Takeyoshi**, Cancer Intelligence Care Systems, Inc., Japan

05 *Reduction of tumor uptake on interim 18F-FBPA-PET predicts the therapeutic response of boron neutron capture therapy*, **Ko-Han Lin**, Department of Nuclear Medicine, Taipei Veterans General Hospital, Taiwan

06 *Assessment of Carotid Invasion of Head and Neck Cancer to be Treated with Boron Neutron Capture Therapy*, **Masatoshi Ohmae**, Oral and maxillofacial Surgery, Rinku General Medical Center, Japan

07 *BNCT is an Effective Salvage Treatment for Recurrent Parotid Adenocarcinoma – A Case Report from Taiwan's BNCT Clinical Trial*, **Yi-Wei Chen**, Division of Radiation Oncology, Department of Oncology, Taipei Veterans General Hospital, Taiwan

08 *BNCT and salvage therapy for a patient with multiform glioblastoma with over seven years survival and preserved performance status*, **Tetsuya Yamamoto**, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Japan

09 *Potential of Boron Neutron Capture Therapy for Malignant Peripheral Nerve Sheath Tumor*, **Takuya Fujimoto**, Department of Orthopaedic Surgery, Hyogo Cancer Center, Japan

10 *Difference in 4-borono-2-18F-fluoro-phenylalanine kinetics between tumor and inflammation in rat model*, **Kohei Hanooka**, Department of Nuclear Medicine and Tracer Kinetics, Osaka University, Japan

11 *Evaluation for Radioactivation of Dental Materials and Draft for Measure Clinical Procedure on BNCT (Part 1) -Cobalt Chrome Alloy*, **Toshiyuki Kubota**, Kubota Dental Clinic, Japan

14:40-16:40 Posters 1, Chemistry (PS1 Ch)

Session Chair: **Rainer Tietze**

01 *Precious metal carborane polymer nanoparticles: potential for Boron Neutron Capture Therapy*, **Nicolas Barry**, University of Warwick, United Kingdom

02 *Synthesis of boron containing magnetic nanoparticles for potential neutron capture therapy*, **Harald Unterweger**, ENT-Department, Section for Experimental Oncology and Nanomedicine (SEON), Else Kröner-Fresenius-Stiftung-Professorship, University Hospital Erlangen, Germany

03 *Gadolinium-loaded Chitosan Nanoparticles with Phospholipid-PEG Layer for Neutron Capture Therapy*, **Hideki Ichikawa**,

Faculty of Pharmaceutical Sciences, Kobe Gakuin University,
Japan

04 *Development of boron-containing polymeric drug delivery system for Boron Neutron Capture Therapy*, **Cheng-Ying Hsieh**, Department of Chemistry, National Tsing-Hua University, Taiwan R.O.C, Taiwan

05 *Toxicity and boron uptake of carboranyl-containing porphyrin-cored dendrimers*, **Justo Cabrera**, Instituto de Ciencia de los Materiales de Barcelona, ICMAB-CSIC, Spain

06 *Feasible evaluation of WOW emulsion as intra-arterial boron delivery carrier for Neutron Capture Therapy to Hepatocellular Carcinoma*, **Hironobu Yanagie**, Dept. of Innovative Cancer Therapeutics, Meiji Pharmaceutical University, Japan

07 *Novel Phosphonium-Based Gadolinium NCT Agents*, **Mingyue Tang Kardashinsky**, University of Sydney, Australia

14:40-16:40 Posters 1, Physics (PS1 P)

Session Chairs: **Ben Phoenix** & **Elisabetta Durisi**

01 *Evaluation of BNCT in-phantom parameters by response matrix method*, **Yaser Kasesaz**, Nuclear Science and Technology Research Institute (NSTRI), Iran

02 *Optimal neutron spectra calculation in BNCT by Geant4 code*, **Zeinab sadat Badieyan**, Birjand University, Iran

03 *Study on the improvement of depth dose distribution using multiple-field irradiation in boron neutron capture therapy*, **Nozomi Fujimoto**, Kyoto University Research Reactor Institute, Japan

04 *Bioneutronics: thermal scattering in organic tissues and its impact on BNCT dosimetry*, **Ricardo Ramos**, Dan Beninson Institute (IDB), San Martin National University (UNSAM), Argentina

05 *A potential selective radiotherapy for ocular melanoma by sulfur neutron capture*, **Ignacio Porras**, University of Granada, Spain

- 06 *A Study of Effective Dose for Tumor in BNCT*, **Yoshinori Sakurai**, Kyoto University Research Reactor Institute, Japan
- 07 *About radiations from gadolinium at Neutron Capture Therapy*, **Gairatulla Kulabdullaev**, Institute of Nuclear Physics, Uzbekistan
- 08 *Dedicated target based on micro-channel geometry for the generation of neutron beams for BNCT*, **Javier Praena**, Universidad de Sevilla, Centro Nacional de Aceleradores, Spain
- 09 *Application of a statistical model for the evaluation of the gamma dose in BNCT Monte Carlo simulations*, **Ignacio Porras**, University of Granada, Spain
- 10 *Boron Neutron Capture Therapy for Breast Cancer in Pregnancy: A Simulative Dosimetry Estimation Study*, **Hashem Miri Hakimabad**, Ferdowsi University of Mashhad, Iran
- 11 *Experimental trial of measuring spatial distribution of neutrons and gamma rays in BNCT*, **Kenichi Tanaka**, Sapporo Medical University, Japan
- 13 *On the Importance of a Dedicated Beam Monitoring System for BNCT Facilities*, **Shiang-Huei Jiang**, Institute of Nuclear Engineering and Science, National Tsing Hua University, Taiwan
- 14 *Development of the real-time neutron monitor with a LiCAF scintillator*, **Kazuya Taki**, Sumitomo Heavy Industries, Ltd., Japan
- 15 *Measurement of Neutron Parameters in the Neutron Beam exit of IHNI*, **YiGuo Li**, China Institute of Atomic Energy, China
- 16 *Photon-neutron mixed field dosimetry by TLD700 glow curve analysis and its implementation in whole body dose monitoring for BNCT treatments*, **Esteban Fabián Boggio**, Bariloche Atomic Center, Atomic Energy National Commission (CNEA), Argentina
- 17 *Neutron flux assessment of a neutron irradiation facility based on inertial electrostatic confinement fusion*, **Manuel Szejnberg Gonçalves-Carralves**, CNEA, Argentina

20 *Effectiveness of epithermal neutron beam and neutron radiation shielding of samples in BNCT experiments*, **Miroslav Vins**, Research Centre Rez, Czech Republic

21 *Alanine Dosimeter Response Characteristics for Charged Particles in BNCT*, **Tokuhiro Kawamura**, Department of Nuclear Engineering, Kyoto University, Japan

22 *Neutron Spectra Measurements at the research reactor TRIGA Mainz*, **Tobias Schmitz**, Institute for Nuclear Chemistry, University of Mainz, Mainz, Germany

23 *Fricke gel, electron spin resonance and thermoluminescence for integration and inter-comparison of measurements in NCT dosimetry*, **M. Marrale**, Department of Physics and Chemistry, Università degli studi di Palermo, Palermo, Italy and INFN, Istituto Nazionale di Fisica Nucleare, Italy

24 *Dosimetric quantities measured by recombination chambers in low-energy neutron beams*, **Piotr Tulik**, National Centre for Nuclear Research, Poland

25 *Effects of alpha particles irradiation on cell survival for BNCT dosimetric studies*, **Bárbara Smilgys**, Instituto de Física "Gleb Wataghin", UNICAMP, Brazil

26 *Evaluation of TLD 600/700 responses at different irradiation fields*, **Paulo Siqueira**, Instituto de Pesquisas Energéticas e Nucleares, IPEN-CNEN/SP, Brazil

27 *Dosimetry of Mainz reactors by means of ESR dosimetry with alanine added with gadolinium*, **M. Marrale**, Dipartimento di Fisica e Chimica, Viale delle Scienze, Ed.18, I-90128 Palermo, Italy and Gruppo V, INFN, Sezione di Catania, Catania, Italy

28 *Extension of the alpha spectrometry technique for boron measurements in bone*, **Lucas Provenzano**, Comisión Nacional de Energía Atómica (CNEA) and CONICET, Argentina

29 *Characteristics and Application of a Spherical Type Activation-based Detector for Neutron Spectrum Measurements at the THOR BNCT Facility*, **Rong-Jiun Sheu**, Institute of Nuclear Engineering and Science, National Tsing Hua University, Hsinchu, Taiwan

30 *PGNAA system preliminary design and measurement of IHNI*, **Zizhu Zhang**, China Institute of Atomic Energy, China

16:40-18:20 Parallel Physics 2 (Pa P2)

Peilisali

Session Chair: **Paolo Colautti & Hiroki Tanaka**

- 16:40-17:00 **Hiroshi Horiike**, Graduate School of Engineering, Osaka University, Osaka, Japan: *Liquid Li based neutron source for BNCT and science application*
- 17:00-17:20 **Hiroki Tanaka**, Kyoto University Research Reactor Institute, Kyoto, Japan: *Study on the accelerator-based neutron source using Be(p,n) reaction with proton energy of lower than 30 MeV*
- 17:20-17:40 **Jaakko Vainionpaa**, Adelphi Technology, Redwood City, California, U.S.A: *Experiments and simulations using a high flux DD neutron generator*
- 17:40-18:00 **Vadim Skalyga**, Institute of Applied Physics, Nizhny Novgorod, Russia: *Neutron Generator for BNCT Based on High Current ECR Ion Source with Gyrotron Plasma Heating*
- 18:00-18:20 **Elisabetta Durisi**, Università di Torino, Italy: *Design and simulation of an optimized photoconverter for e-linac based neutron source for BNCT research*

MON

16:40-18:20 Parallel Boron Imaging 1 (Pa B11)

Pörssisali

Session Chairs: **Agustina Portu & Allah Detta**

- 16:40-17:00 **Allah Detta**, Department of Neurosurgery, Queen Elizabeth Hospital Birmingham & School of Cancer Sciences, University of Birmingham: *Detection of cellular boron in human glioblastoma biopsies after infusion of BPA*
- 17:00-17:20 **Chunlei Bi**, Research and Development Office, Japan Chemical Analysis Center, Chiba, Japan: *A method for individual quantitation of the combined boronophenylalanine and borocaptate by liquid chromatography-electrospray ionization-mass spectrometry*
- 17:20-17:40 **Yurie Yamaguchi**, Research and Development Office, Japan Chemical Analysis Center, Chiba, Japan: *Development of rapid and precise boron isotope analysis in whole blood by HR-ICP-MS*
- 17:40-18:00 **Keiji Saito**, Department of Chemistry, Faculty of science, Shinshu University, Matsumoto, Japan: *Parameter optimization for the determination of BSH in whole blood by ¹⁰B-NMR*
- 18:00-18:20 **Kazuo Yoshino**, Department of Chemistry, Faculty of science, Shinshu University, Matsumoto, Japan: *First observation of the complex of BPA with blood component in whole blood by ¹⁰B-NMR*

MON

16:40-18:00 Parallel Chemistry 2 (Pa Ch2)

Börs-kabinetti

Session Chairs: **Hiroyuki Nakamura** & **Satish Jalisetgi**

- 16:40-17:00 **Alexander Zaboronok**, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan: *Hyaluronic acid- and melanin-based boron compounds for combined neutron capture therapy*
- 17:00-17:20 **Ming-Hua Hsu**, Nuclear Science & Technology Development Center, National Tsing Hua University, Taiwan: *Development of Boron-Containing Nanodiamonds for Boron Neutron Capture Therapy*
- 17:20-17:40 **Rainer Tietze**, ENT-Department, Section for Experimental Oncology and Nanomedicine, University Hospital Erlangen, Germany: *Boron containing magnetic nanoparticles for neutron capture therapy - An innovative approach for specifically targeting tumors*
- 17:40-18:00 **Tooru Andoh**, Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University, Kobe, Japan: *Effect of particle size of nanoparticulate L-BPA formulation on biodistribution of ¹⁰B after its intratumoral administration to tumor-bearing mice*

18:30-20:00 ISNCT Working Group meetings

MON

Tuesday June 17th

9:00-11:00 Parallel Physics 3 (Pa P3)

Peilisali

Session Chair: **Sergey Taskaev**

- 9:00-9:20 **Paul Farrell**, GT Advanced Technologies, Danvers, MA, Canada: *Hyperion™ Accelerator Technology for Boron Neutron Capture Therapy*
- 9:20-9:40 **Daniel M. Minsky**, Comisión Nacional de Energía Atómica (CNEA) - Escuela de Ciencia y Tecnología, Universidad de San Martín (ECyT, UNSAM) - Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina: *Near threshold ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction as a neutron source for BNCT*
- 9:40-10:00 **Shlomi Halfon**, Soreq NRC, Yavne - Racah Institute of Physics, Hebrew University, Jerusalem, Israel: *High-Power Proton Irradiation and Neutron Production with a Liquid-Lithium Target for Accelerator-based BNCT*
- 10:00-10:20 **Ben Phoenix**, School of Physics and Astronomy, University of Birmingham, Birmingham, UK: *Development of a higher power cooling system for solid lithium targets*
- 10:20-10:40 **Tianjiao Liang**, Beijing National Laboratory for Condensed Matter Physics, Institute of Physics, Chinese Academy of Sciences, Beijing, China: *Design of Neutron Production Target and Beam Shaping Assembly for 3.5MeV RFQ Accelerator-based BNCT*
- 10:40-11:00 **Javier Praena**, Universidad de Sevilla, Centro Nacional de Aceleradores, Spain: *Experimental study of the 13.5 keV resonance of the ${}^{33}\text{S}(n,\alpha){}^{30}\text{Si}$ reaction at CERN n_TOF facility for BNCT*

TUE

9:00-11:00 Parallel Physics 4 (Pa P4)

Börs-kabinetti

Session Chairs: **Grazia Gambarini & Yuan-Hao Liu**

- 9:00-9:20 **Yaser Kasesaz**, Nuclear Science and Technology Research Institute (NSTRI), Iran: *Design and construction of BNCT irradiation facility at Tehran research reactor*
- 9:20-9:40 **Michał Aleksander Gryziński**, National Centre for Nuclear Research, Otwock-Świerk, Poland: *Epi-thermal neutron source at MARIA reactor*
- 9:40-10:00 **Isao Murata**, Graduate School of Engineering, Osaka University, Osaka, Japan: *Mock-up Experiment at Birmingham University for BNCT Project of Osaka University - Outline of the Experiment*
- 10:00-10:20 **Yaser Kasesaz**, Nuclear Science and Technology Research Institute (NSTRI), Iran: *Construction of a convenient head phantom for BNCT experiments at Tehran research reactor*
- 10:20-10:40 **Grazia Gambarini**, Department of Physics, Università degli Studi di Milano, Milan - INFN, Istituto Nazionale di Fisica Nucleare, Italy: *Study of suitability of Fricke-gel-layer dosimeters for in-air measurements to characterise epi-thermal/thermal neutron beams for NCT*
- 10:40-11:00 **Haruaki Ueda**, Graduate School of Engineering, Kyoto University, Kyoto, Japan: *The improvement of the energy resolution in epi-thermal region of Bonner sphere using boric acid solution moderator*

9:00-11:00 Parallel Boron Imaging 2 (Pa BI2)

Pörssisali

Session Chairs: **Daniel M. Minsky** & **Shiang-Huei Jiang**

- 9:00-9:20 **Fong-In Chou**, Nuclear Science and Technology Development Center - Institute of Nuclear Engineering and Science, National Tsing Hua University, Hsinchu, Taiwan: *Autoradiographic and histopathological studies of boric acid-mediated BNCT in hepatic VX2 tumor-bearing rabbits: specific boron retention and damage in tumor and tumor vessels*
- 9:20-9:40 **Agustina Portu**, Comisión Nacional de Energía Atómica - Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina: *Neutron autoradiography in nuclear track detectors: simultaneous observation of cells and nuclear tracks from BNC reaction by UV C sensitization of polycarbonate,*
- 9:40-10:00 **Agustina Portu**, Comisión Nacional de Energía Atómica - Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina: *Inter-comparison project for boron concentration determination at INFN-University of Pavia (Italy) and CNEA (Argentina)*
- 10:00-10:20 **Chun-Kai Huang**, Institute of Nuclear Engineering and Science, National Tsing Hua University, Hsinchu, Taiwan: *Improvement of a PGNAA Facility for BNCT in THOR*
- 10:20-10:40 **Masanobu Manabe**, Division of Electrical, Electronic and Information Engineering, Graduate School of Engineering, Osaka University, Osaka, Japan: *Basic property of array-type CdTe detector for BNCT-SPECT*
- 10:40-11:00 **Alexander Winkler**, Department of Physics, University of Helsinki, Finland: *Detecting BNCT prompt gamma and neutron spectra with a CdTe detectors*

11:00-11:30 Coffee

11:30-12:30 Invited lecture PET Imaging

- **Heikki Minn**, MD, Professor of Oncology, Turku University Hospital, Turku, Finland: *PET as a research tool in oncology*

12:30-13:30 Lunch

12:30-18:30 Tour to Söderskär Light House

19:00 Reception at the Town Hall

TUE

Wednesday June 18th

9:00-10:00 Plenary Biology 2 (PI B2)

Pörssisali

Session Chairs: **Rolf Barth** & **Mandy Schwint**

- 9:00-9:20 **Amanda E Schwint**, CNEA, Argentina: *Boron Neutron Capture Therapy (BNCT) Mediated by Boronated Liposomes for Oral Cancer in the Hamster Cheek Pouch Model*
- 9:20-9:40 **Andrea Monti Hughes**, CNEA, Argentina: *Preliminary study of "Sequential" BNCT in an oral precancer model: a novel BNCT approach to treat tumors and inhibit the development of second primary tumors from surrounding precancerous tissue*
- 9:40-10:00 **Silva Bortolussi**, Department of Physics, University of Pavia - Istituto Nazionale di Fisica Nucleare (INFN), Section of Pavia, Italy: *First results of pre-clinical studies of BNCT for Osteosarcoma*

10:00-11:00 Plenary Physics 1 (PI P1)

Pörssisali

Session Chairs: **Saverio Altieri** & **Silva Bortolussi**

- 10:00-10:20 **Hiroaki Kumada**, University of Tsukuba, Japan: *Verification of Tsukuba Plan, a new treatment planning system for BNCT*
- 10:20-10:40 **Yen-Wan Hsueh Liu**, National Tsing Hua University, Taiwan: *BNCT Treatment Planning for Superficial and Deep-Seated Tumors : Experience from Clinical Trial of Recurrent Head and Neck Cancer at THOR*
- 10:40-11:00 **Sara González**, Comisión Nacional de Energía Atómica (CNEA) & Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina: *The first clinical BNCT assessment through TCP calculations based on the novel concept of photon isoeffective dose*

11:00-11:30 *Coffee*

11:30-12:30 *Invited lecture clinical*

- **Jyrki Törnwall**, MD., PhD., Docent, Specialist in Oral and Maxillofacial Surgery, Department of Oral and Maxillofacial Surgery, Surgical Hospital, Helsinki University Central Hospital, Helsinki, Finland

12:30-13:30 *Lunch*

13:30-15:10 *Parallel Physics 5 (Pa P5)*

Peilisali

Session Chairs: **Sara González** & **Hiroaki Kumada**

- 13:30-13:50 **Shintaro Ishiyama**, Quantum Beam Science Directorate, Japan Atomic Energy Agency, Japan: *Deterministic parsing model of CBE factor for Intracellular 10B Distribution in Boron Neutron Capture Therapy*
- 13:50-14:10 **Ian Postuma**, University of Pavia and INFN, Italy: *Geant4 study of BNCT mixed field energy deposit in an approximated healthy tissue geometry*
- 14:10-14:30 **Ignacio Porras**, University of Granada, Spain: *Weighted-Kerma/Fluence Factors for Monte Carlo calculations of the Biological Dose in BNCT*
- 14:30-14:50 **Juan Manuel Longhino**, CNEA, IB, Argentina: *Calculation evaluation of Brachyenhancers as a complementary dose delivery system for BNCT application*
- 14:50-15:10 **Esteban Fabián Boggio**, Bariloche Atomic Center, Atomic Energy National Commission (CNEA), Argentina: *Beta Enhancers: towards a new implementation for BNCT on superficial tumors*

13:30-15:10 Parallel Clinical 1 (Pa C1)

Pörssisali

Session Chairs: **Wolfgang Sauerwein & Laura Evangelista**

- 13:30-13:50 **Desire Ngoga**, University of Birmingham, UK: *Who benefits most of BNCT? – A review on literature data on the prognostic value of protein expression of amino acid transporter 4F2hc/LAT1*
- 13:50-14:10 **Shin-Ichi Miyatake**, Department of Neurosurgery, Osaka Medical College, Japan: *BNCT for recurrent malignant gliomas, with the special combination of bevacizumab*
- 14:10-14:30 **Shinji Kawabata**, Department of Neurosurgery, Osaka Medical College, Japan: *Clinical results of Boron neutron capture therapy for the patients with malignant meningioma*
- 14:30-14:50 **Yu-Ming Liu**, Division of Radiation Oncology, Taipei Veteran General Hospital, Taiwan: *The 18F-BPA-PET SUV data as a prognostic factor for BNCT treatment failure: from clinical experience*
- 14:50-15:10 **Teruhito Aihara**, Proton Medical Research Centre, University of Tsukuba, Japan: *A simple strategy to decrease the incidence of fatal carotid blowout syndrome after BNCT for head and neck cancers*

13:30-15:10 Parallel Biology 2 (Pa B2)

Börs-kabinetti

Session Chair: **Gen Futamura**

- 13:30-13:50 **Natalya Gubanova**, Institute of Cytology and Genetics, SB RAS, Russian Federation: *Evaluation of micronucleation and viability of glioma cells in vitro neutron beams irradiated*
- 13:50-14:10 **Mitsuko Masutani**, Division of Genome Stability Research, National Cancer Center Research Institute, Japan: *Analysis of cell-death response and DAMPs after boron neutron capture reaction in human cancer cells*

- 14:10-14:30 **Norio Miyoshi**, Tumor Pathology, Faculty of Medicine, University of Fukui, Japan: *Three In One: A Multifunctional Antitumor Sensitizer for Photodynamic, Boron Neutron Capture and Proton Therapies*
- 14:30-14:50 **Yuko Kinashi**, Research Reactor Institute, Kyoto University, Japan: *The influence of the p53 status for biological effects of the glioblastoma cells following boron neutron capture therapy*
- 14:50-15:10 **Marina Carpano**, Radiobiology Department (CAC), National Atomic Energy Commission (CNEA), Argentina: *Optimization of Boron Neutron Capture Therapy (BNCT) for the Individual Treatment of Cutaneous Melanoma*

15:10-17:10 Poster Sessions 2 & Coffee

Linnanpiha

15:10-17:10 Posters 2, Biology (PS2 B)

- 01 *BNCT as a potential therapy for rheumatoid arthritis: biodistribution study of BPA and GB-10 in a model of antigen-induced arthritis in rabbits*, **Verónica A Trivillin**, CNEA, Argentina
- 02 *Significance of Combined Treatment with Bevacizumab in Boron Neutron Capture Therapy in Terms of Local Tumor Response and Lung Metastasis*, **Shin-ichiro Masunaga**, Research Reactor Institute, Kyoto University, Japan
- 03 *Research of Influence of Boron-Capture Reaction on Transport Proteins of Human Blood Serum*, **Gairatulla Kulabdullaev**, Institute of Nuclear Physics, Uzbekistan
- 04 *Detection of plasmid strand breaks in boron neutron capture reaction*, **Emiko Okamoto**, Department of Neurosurgery, Master's program in Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan
- 05 *Therapeutic Efficacy of Boric Acid-Mediated Boron Neutron Capture Therapy for Liver Tumors in a VX2 Multifocal*

Liver Tumor-bearing Rabbit Model, **Fong-In Chou**, Institute of Nuclear Engineering and Science, Nuclear Science and Technology Development Center, National Tsing Hua University, Hsinchu, Taiwan

06 *Continuous infusion of low-dose BPA to maintain a high boron concentration in tumor and narrow down the range of normal tissue to blood boron ratios for BNCT in a mouse model*, **Fong-In Chou**, Institute of Nuclear Engineering and Science and Nuclear Science and Technology Development Center National Tsing Hua University, Hsinchu, Taiwan

07 *Additive effect of BPA and Gd-DTPA for application in accelerator-based neutron source*, **Fumiyo Yoshida**, Faculty of Medicine, University of Tsukuba, Japan

08 *Experimental trial of establishing brain necrosis mouse model using proton beam*, **Natsuko Kondo**, Kyoto University, Japan

09 *Localized Dose Delivering by Ion Beam Irradiation for Experimental Trial of Establishing Brain Necrosis Model*, **Takushi Takata**, Research Reactor Institute, Kyoto University, and The Wakasa Wan Energy Research Center, Japan

10 *Prospects of intercellular complexes with gadolinium application in Binary Radiotherapy*, **Alexey Lipengolts**, Blokhin Russian Cancer Scientific Centre, Russian Federation

11 *Novel multi-linked mercaptoundecahydrododecaborate (BSH) fused cell-penetrating peptide accelerated boron neutron capture therapy (BNCT)*, **Hiroyuki Michiue**, Department of Physiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan

12 *Preparation, Characterization and Evaluation of Boron-modified Diblock Copolymer as Vehicle for Boron Neutron Capture Therapy*, **Jiun-Yu Chen**, Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes, Taiwan

13 *In Vitro Studies of Cellular Response to DNA Damage Caused by Boron Neutron Capture Therapy (BNCT) in a Recurrent Thyroid Carcinoma*, **Carla Rodríguez**, Radiobiology Department (CAC), National Atomic Energy Commission (CNEA), Argentina

14 *Preliminary in vivo studies for the application of Boron Neutron Capture Therapy (BNCT) to the treatment of differentiated and recurrent thyroid carcinoma using the histone deacetylase inhibitor, sodium butyrate (NaB) as a radiosensitizer*, **Carla Rodríguez**, Radiobiology Department (CAC), National Atomic Energy Commission (CNEA), Argentina

15:10-17:10 Posters 2, Boron Imaging (PS2 BI)

01 *New approach to real-time measurement of the number of $^{10}\text{B}(n,\alpha)^7\text{Li}$ reactions using Gaseous Electron-Tracking Compton Camera (ETCC) system in boron neutron capture therapy*, **Satoshi Nakamura**, National Cancer Center, Japan

02 *Autoradiography for cell culture testing: Preliminary Results*, **Catrin Grunewald**, Institut für Kernchemie, Johannes Gutenberg University, Germany

03 *Application of micro-PIXE/PIGE technology to boron concentration analysis*, **Kei Nakai**, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Japan

15:10-17:10 Posters 2, Physics (PS2 P)

Session Chairs: **Javier Praena** & **Esteban Fabián Boggio**

01 *Mock-up Experiment at Birmingham University for BNCT Project of Osaka University - Neutron Flux Measurement with Gold Foil*, **Shingo Tamaki**, Graduate School of Engineering, Osaka University, Japan

02 *Design of A New Wide-dynamic-range Neutron Spectrometer for BNCT with Liquid Moderator and Absorber*, **Shingo Tamaki**, Division of Electrical, Electronic and Information Engineering, Graduate School of Engineering, Osaka University, Japan

03 *Mock-up Experiment at Birmingham University for BNCT Project of Osaka University - Gamma-ray Dose Measurement with Glass Dosimeter*, **Sachiko Yoshihashi**, Graduate School of Engineering, Osaka University, Japan

04 *Neutron Intensity Monitor with Activation Foil for $p\text{-Li}$ Neutron Source for BNCT*, **Isao Murata**, Osaka University, Japan

05 *Potential application of NIPAM polymer gel for dosimetric purposes in BNCT*, **Yaser Kasesaz**, Nuclear Science and Technology Research Institute (NSTRI), Iran

06 *Problems of neutron spectrum measurements with TOF technique and their solutions*, **Alexandr Makarov**, Budker Institute of Nuclear Physics, Russian Federation

07 *n _TOF (CERN) planning experiments to improve BNCT dosimetry: $^{35}\text{Cl}(n,p)$ and $^{14}\text{N}(n,p)$ cross section measurements*, **Marta Sabaté-Gilarte**, Universidad de Sevilla, Spain - CERN Switzerland

08 *Experimental study of the 13.5 keV resonance of the $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ reaction at CERN n _TOF facility for BNCT*, **Javier Praena**, Universidad de Sevilla. Centro Nacional de Aceleradores, Spain

09 *Design of epithermal and thermal neutron beams for accelerator based BNCT applying to the TRIGA-II research reactor facility (1) Cyclotron accelerator (proton energy 30MeV and electric current 1mA)*, **Tetsuo Matsumoto**, Tokyo City University, Japan

10 *Design of epithermal and thermal neutron beams for accelerator based BNCT applying to the TRIGA-II research reactor facility (2) Linac accelerator (proton energy 8MeV and electric current 10mA)*, **Tetsuo Matsumoto**, Tokyo City University, Japan

11 *Feasibility study of using laser accelerator to produce appropriate neutron beam for BNCT: MCNP Simulation*, **Yaser Kasesaz**, Nuclear Science and Technology Research Institute (NSTRI), Iran

12 *Investigation on the reflector/moderator geometry and its effect on the neutron beam performance in BNCT*, **Yaser Kasesaz**, Nuclear Science and Technology Research Institute (NSTRI), Iran

13 *Design of Photon Converter and Photoneutron Target for High Power Electron Accelerator Based BNCT*, **Faezeh Rahmani**, Department of Radiation Application, Shahid Beheshti University, Iran

- 14 *Modification of the argon stripping target of the tandem accelerator*, **Sergey Taskaev**, Budker Institute of Nuclear Physics, Novosibirsk, Russian Federation
- 15 *A new concept of a Vacuum Insulation Tandem Accelerator*, **Sergey Taskaev**, Budker Institute of Nuclear Physics, Novosibirsk, Russian Federation
- 16 *Studying of gamma-ray and neutron radiation in case of 1–2 MeV proton beam interaction with various construction materials*, **Sergey Taskaev**, Budker Institute of Nuclear Physics, Russian Federation
- 17 *Development of an accelerator-driven compact neutron source for BNCT in Nagoya University*, **Kazuki Tsuchida**, Nagoya University, Japan
- 18 *Study on the design of the miniature cyclotron for accelerator based BNCT*, **YiGuo Li**, China Institute of Atomic Energy, China
- 19 *Development of the injector for Vacuum Insulated Tandem Accelerator*, **A. Kuznetsov**, Budker Institute of Nuclear Physics, Russian Federation
- 20 *Optimum design of a beam shaping assembly with an accelerator-driven subcritical neutron multiplier for boron neutron capture therapies*, **Fujio Hiraga**, Hokkaido University, Japan
- 21 *Optimal moderator materials at various proton energies considering residual radioactivity for an accelerator-driven $^9\text{Be}(p,n)$ BNCT neutron source*, **Yuka Hashimoto**, Graduate School of Engineering, Hokkaido University, Japan
- 22 *Neutron Activation and Exposure Estimation of a Lithium Target Design*, **Yuan-Hao Liu**, Independent Researcher, Taiwan
- 23 *A comprehensive study on $^9\text{Be}(d,n)^{10}\text{B}$ -based neutron sources for skin and deep tumor treatments*, **María E. Capoulat**, Comisión Nacional de Energía Atómica, Argentina
- 24 *Progress in the design and development of a neutron production target for Accelerator-Based Boron Neutron Capture Therapy*, **Leonardo Gagetti**, CONICET, CNEA, Argentina
- 25 *A beam line for BNCT at the European Spallation Source ESS* Wolfgang Sauerwein, University Duisburg-Essen, University Hospital Essen, Germany

- 26 *Safety analysis of the uranium neutron converter for BNCT facility*, **Michał Aleksander Gryziński**, National Centre for Nuclear Research, Poland
- 27 *Design of an epithermal BNCT system using a compact coolant moderated neutron generator*, **Allan Chen**, Adelphi Technology Inc, United States
- 28 *Decisions and Preparations for a Rapid Shutdown and Decommissioning of the Finnish TRIGA FIR 1*, **Jiri Auterinen**, VTT Technical Research Centre of Finland, Finland
- 29 *Narrow Neutron Beam Assembly Facility in BNCT Application*, **Ali Pazirandeh**, Science and Research Branch, Islamic Azad University, Iran
- 30 *A study of photoneutron source based on electron accelerator including heat transfer using the jet impingement cooling method*, **Mansoureh Tatari**, Faculty of Physics, University of Yazd, Yazd, Iran

Thursday June 19th

9:30-10:30 Parallel Physics 6 (Pa P6)

Pörssisali

Session Chair: **Ignacio Porras & Nicoletta Protti**

- 9:30-9:50 **Tobias Schmitz**, Institut for Nuclear Chemistry, University of Mainz, Mainz, Germany: *The Response of ESR Dosimeters in Thermal Neutron Fields*
- 9:50-10:10 **Saverio Altieri**, Department of Physics University of Pavia and INFN, Italy: *Determination of gamma component in thermal column of Pavia Triga reactor by using alanine ESR detectors*
- 10:10-10:30 **Maurizio Marrale**, Dipartimento di Fisica e Chimica, Viale delle Scienze, Ed.18, I-90128 Palermo, Italy and Gruppo V, INFN, Sezione di Catania, Catania, Italy: *Phenol compounds for Electron Spin Resonance dosimetry of gamma and neutron beams*

9:30-10:30 Parallel Chemistry 3 (Pa Ch3)

Peilisali

Session Chairs: **Madleen Busse & Po-Shen Pan**

- 9:30-9:50 **Satish Jalisatgi**, International Institute of Nano and Molecular Medicine, School of Medicine, University of Missouri, Columbia, USA: *Boron-rich Liposomes as Nanoscale Delivery Agents for BNCT*
- 9:50-10:10 **Yoshihide Hattori**, Research Center of Boron Neutron Capture Therapy, Research Organization for the 21st Century, Osaka Prefecture University, Nakaku, Sakai, Japan: *Design and Synthesis of Tumor Seeking closo-Dodecaborate-Containing Amino Acids as Boron Carrier for BNCT*
- 10:10-10:30 **Takeshi Nagasaki**, Graduate School of Engineering, Osaka City University, Japan: *Carborane-Kojic Acid Conjugate for Melanoma-Targeting Boron Neutron Capture Therapy*

10:30-11:00 *Coffee*

11:00-12:00 *Plenary Physics 2 (PI P2)*

Pörssisali

Session Chairs: **Stuart Green** & **Hanna Koivunoro**

- 11:00-11:20 **Hiroaki Kumada**, Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan: *Development of the linac based NCT facility in iBNCT project*
- 11:20-11:40 **Yoshihisa Abe**, Department of Radiation Oncology, National Cancer Center, Tokyo, Japan: *Development of treatment couch with computer controlled 5-axis movements – For clinical use in the accelerator-based BNCT*
- 11:40-12:00 **Sara J. González**, Comisión Nacional de Energía Atómica (CNEA) - Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina: *Ex-situ lung BNCT at RA-3 Reactor: computational dosimetry and boron biodistribution study*

12:00-12:45 *Roundtable & Closing*

12:45-13:45 *Lunch*

14:00-17:00 *Tour to Otaniemi: FiR 1 excursion and presentation seminar on European Spallation Source (ESS)*

Abstracts

Sunday June 15th 2014

Hatanaka Lecture

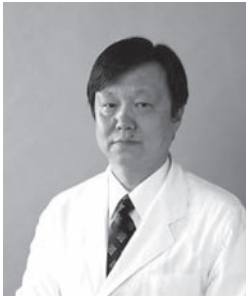
Development of BNCT in 12 years at Osaka Medical College

S. Miyatake¹, S. Kawabata¹, R. Hiramatsu¹, K. Yokoyama¹, A. Doi¹, K. Onishi¹, S. Miyata¹, Y. Kuroda¹, Y. Hirota¹, G. Futamura¹, T. Kuroiwa¹ and K. Ono²

¹Department of Neurosurgery, Osaka Medical College

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Shin-Ichi Miyatake, M.D., Ph.D.

Since January 2002, we applied BNCT for malignant brain tumors with many collaborators. In this presentation, let us introduce the development of BNCT in these 12 years at Osaka Medical College. As of February 2014, we have applied reactor-based BNCT for 58 cases of newly diagnosed GBM, 45 cases of recurrent malignant gliomas, 30 cases of recurrent high grade meningiomas, and so on, totally 139 cases with 156 times BNCT.

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

After the confirmation of the drastic effects of this unique tumor-selective particle irradiation for recurrent malignant gliomas, next we applied this technology to newly diagnosed GBM with the additional XRT boost. A pilot study using BNCT and XRT without TMZ showed median survival time (MST) as 23.5 months for newly diagnosed GBM. Then we started and maintain the multi-center phase 2 clinical trial for newly diagnosed GBM using BNCT, XRT and temozolomide as anti-tumor agent as a clinical trial, supported by MHLW (one of the department of Japanese Government).

Then we applied BNCT for recurrent high grade meningiomas. The patient numbers of high grade meningiomas treated by BNCT is most prominently increasing in our recent BNCT series. Especially malignant meningiomas (WHO grade 3) cannot be controlled even with, repetitive surgeries and irradiations including XRT and SRS. High grade meningiomas seemed to be a good candidate for BNCT, however, out of field recurrence, systemic metastasis, CSF dissemination are still major problems. Also almost all cases were treated by former repetitive radiation as described above, the control of radiation necrosis has been a challenge.

Irrespective of tumor types, we adopted air instillation technique for deep seated tumor with large tumor-removed cavity, to penetrate a enough neutron beam and to improve the minimum tumor dose. Also we applied anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab aggressively for the treatment of symptomatic radiation necrosis and symptomatic pseudoprogression, after BNCT especially for the recurrent cases who had already treated by other radiation modality. Almost these improvements were attempted for the first time in the world from our department and collaborators.

Based on these reactor-based BNCT experiences and results for malignant brain tumors, now we are applying accelerator-based BNCT for recurrent malignant gliomas with KUR team and companies, as a clinical trial to obtain on-label use from MHLW, since October 2012.

Shin-Ichi Miyatake, M.D., Ph.D. - Education and Professional Activities

- 1980 M.D., Kyoto University Medical School
- 1980-83 Residency, Department of Neurosurgery, Kyoto University
- 1984-87 Graduate School of Medicine, Kyoto University
- 1988-94 Instructor, Department of Neurosurgery, Kyoto University
- 1995-96 Research Fellow, Department of Neurosurgery, Georgetown University
- 1997-2000 Assistant Professor, Department of Neurosurgery, Kyoto University
- 2001-2012 Associate Professor, Department of Neurosurgery,
Osaka Medical College
- 2012-2014 Professor, Department of Neurosurgery, Osaka Medical College
- 2014- Professor, Cancer Center, Osaka Medical College

Membership of academic societies

Japan Neurosurgical Society (board-certified Councilor)
Japan Society of Gene Therapy (Councilor)
Japan Society of Neuro-Oncology (Councilor)
Japan Society of Regenerative Medicine (Councilor)
Japan Society of Boron Neutron Capture Therapy (Councilor)
Japan Society of Molecular Neurosurgery (Councilor)
Japan Cancer Association

Awards and Patents

The 8th Galenus Prize from the Japan Neurosurgical Society in 1989.
United States Patent (5728379) "Tumor-or Cell-Specific Herpes Simplex Virus Replication" granted on March 17, 1998.

BNCT Activities

Became involved in BNCT in 1997 with Prof. Ono and Oda, when the Instructor of Dept. of Neurosurgery.
Treat more than 160 cases of brain tumors with reactor-based BNCT.
Organized the 6th Japanese Society of Boron Neutron Capture Therapy and the 27th Japanese Society of Neuro-Onocology in 2009.
Organized multi-center clinical trial for newly diagnosed GBM using BNCT from 2009.
Participate in acceralator-based BNCT, phase-1 clinical trail for recurrent malignant gliomas from 2012, as the responsible clinical medical doctor.
Author/co-author of well over 100 publications/books in BNCT.

PI C1 01

Boron Neutron Capture Therapy in Patients with Recurrent Head and Neck Cancers Who Have No Other Treatment Options

J. Kato¹, Y. Fujita², M. Ohmae³, Y. Sakrai⁴, M. Suzuki⁴, I. Murata⁵, H. Horiike⁵, T. Sumi¹, S. Iwai¹, M. Nakazawa¹, Yoshiaki Yura¹ and K. Ono⁴

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⁴Radiation Oncology Research Laboratory, Research Reactor Institut, Kyoto University, Osaka, Japan ⁴ Japan, ⁵Division of Electrical, Electronic and Information Engineering, Graduate School of Engineering, Osaka University, Japan

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 February, 2013, we have treated a total of 35 patients with recurrent HNC by means of 52 applications of BNCT. Histopathologically, there were 24 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 35 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 17 of 35 (53%) had regional lymph node metastases and 10 out of 35 (29%) 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, 2.5-4.0 for sarcomas and 2.5-3.7 for parotid tumors. (1) Regression rates were CR: 18 patients (51 %), PR: 13

(37%), PD: 3 (9%), and not evaluated (NE): 1 patient. The overall patient response rate was 88%. (2) The Mean Survival Time was 24.2 months and the 4 year and 7-year OS rates were 42% and 36%, respectively. (3) Survival times following BNCT ranged from 1 to 95 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.

PI C1 02

Fractionated BNCT for locally recurrent head and neck cancer at THOR: an update for treatment results

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Introduction

To report the results of fractionated boron neutron capture therapy (BNCT) for treatment of recurrent Head & Neck cancer patients after conventional radiotherapy at Tsing Hua Open-Pool Reactor (THOR) in Taiwan.

Materials and Methods

From 2010 to 2014, seventeen patients (M/F=15/2, median age 56 Y/O) were enrolled for this phase I/II clinical trial. Previous accumulated RT dose ranged from 63 to 136.4 Gy. BNCT was performed with boronophenylalanine (BPA)-fructose (400 mg/kg) injected intravenously in 2 phases. Two-fraction treatment at 28-day interval was scheduled for each patient. Before each fraction of treatment, BPA-PET scan was done to determine the Tumor/Normal tissue (T/N) ratio for each tumor. In-house designed THORplan was the treatment planning system. CT simulations were performed before each fraction and tumors were recontoured. Prescription dose (or V80) was intended to cover 80% of Gross Tumor Volume (GTV) by dose volume histogram (DVH) while limiting mucosa volume receiving > 10 Gy (Eq) as low as possible. Tumor responses were assessed using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria v1.1 and adverse effects using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results

Total 23 tumors were treated. Median T/N ratios was 3.4 (range 2.5 to 6.3) for the first fraction and 2.0 (range 1.8 to 2.8) for the second fraction. Median V80 dose was 19.8 (range 11.6 to 36.9) Gy (Eq) for the first fraction and 12.95 (range 3.8 to 22.1) Gy (Eq) for the second fraction. All except two cases received 2 fractions of BNCT as planned. Median interval between 2 fractions was 28 (range 26 to 33)

days. After a median follow-up time of 9.7 (range 2.1 to 35.4) months, 6 patients had complete response (CR), 6 had partial response, 2 had stable disease, 3 had progression of disease. Common acute toxicities included mucositis, alopecia, and radiation dermatitis. No Gr IV or worse toxicity observed. Five of six tumors receiving total V80 dose > 40 Gy (Eq) had CR while only one of six tumors receiving total V80 dose < 25 Gy (Eq) had CR. Two-year overall survival was 45 %. Two-year local progression-free survival was 27 %. The overall survival for tumors of nasal cavity/paranasal sinus and nasopharynx was better than those of other sites (p=0.0059).

Conclusion

Fractionated BNCT at 28-day interval with adaptive planning according to changed T/N ratios and tumor volumes seems to be effective and safe for selected recurrent head & neck cancer in this trial.

PI C1 03

Clinical Experiences of Boron Neutron Capture Therapy to Recurred Rectal Cancers

Hironobu Yanagie^{1,2,3}, Kazuyuki Oyama^{1,4}, Ryo Hatae⁴, Syoji Maruyama⁴, Yasuo Ohno⁴, Shinichi Kurokawa⁵, Yasumasa Nonaka^{1,6}, Hirotaka Sugiyama^{1,7}, Yoshitaka Furuya^{1,8}, Keiko Taniike⁹, Minoru Suzuki¹⁰, Shin-ichiro Masunaga¹⁰, Tomoko Kinashi¹⁰, Yoshinori Sakurai¹⁰, Natsuko Kondo¹⁰, Masaru Narabayashi¹⁰, Hiroki Tanaka¹⁰, Akira Maruhashi¹⁰, Koji Ono¹⁰, Jun Nakajima^{11,3}, Minoru Ono^{12,3}, Hiroyuki Takahashi^{2,3}, and Masazumi Eriguchi^{1,4}

¹Dept. of Innovative Cancer Therapeutics, Meiji Pharmaceutical University, Tokyo, ²Dept. of Nuclear Engineering & Management, School of Engineering, The University of Tokyo, Tokyo, ³Cooperative Unit of Medicine & Engineering, The University of Tokyo Hospital, Tokyo, ⁴Japan Anti-Tuberculosis Association, Shin-Yamate Hospital, Tokyo, ⁵Dept. of Surgery, Fuchinobe General Hospital, Kanagawa, ⁶Dept. of Surgery, Keiaikai Hoyo Hospital, Iwate, ⁷Dept. of Internal Medicine, Muro-kai, Takaoka North Asahi Clinic, Shizuoka, ⁸Dept. of Surgery, Satukidai Hospital, Chiba, ⁹Dept. of Radiology, Nishijin Hospital, Kyoto, ¹⁰Research Reactor Institute, Kyoto University, Osaka, ¹¹Dept. of Respiratory Surgery, The University of Tokyo Hospital, Tokyo, ¹²Dept. of Cardiac Surgery, The University of Tokyo Hospital, Tokyo, JAPAN

Introduction

Applications of boron neutron-capture therapy (BNCT) has been expanded to a lot of cancer cases in clinically. We started the pilot clinical studies of BNCT to recurred breast cancer, hepatic cancer, and gastrointestinal cancers. In this paper, we present our experienced pilot clinical studies of BNCT in patients of rectal cancer.

Case Reports and Discussions

We had applied BNCT for the treatment of recurred rectal cancer.

[Case 1] 51-year-old woman with rectal cancer had been performed low anterior resection with lymph node (LN) dissection, and administrated mFOLFOX6 and BV, and performed radiation therapy (total 50Gy). In spite of additional Hartmann's operation with sacral bone partial resection, the recurrence in pelvic cavity was recognized, and then sciatic neuralgia and walking disturbance were occurred. The high accumulating images of tumour in pelvic cavity was acquired

by ^{18}F labeled ^{10}BPA PET. The tumour / blood ratio was 2.6. The pre-BNCT dosimetry was performed using SERA (more than 90% of tumour fluence is 20Gy-Eq on BNCT, and maximum fluence of normal mucosa of small intestine, caudal nerve, and mucosa of urinary bladder are 7.3, 8.9, 4.3 Gy-Eq, respectively). The tumour growth was regulated during 2 months by BNCT. The pain of left leg and sacral portion were markedly improved 2 weeks after BNCT.

[Case 2] 56-year-old woman with rectal cancer had been performed low anterior resection with lymph node (LN) dissection, administered mFOLFIRI, and performed radiation therapy (total 50Gy). In spite of adjuvant therapies, the tumour had regrowed, and sciatic neuralgia and local oozing in pelvic cavity were recognized. The tumour / blood ratio of tumour in pelvic cavity acquired by ^{18}F labeled ^{10}BPA PET was 2.9. The neutron dose of 82 % tumour area was 15 Gy-Eq, and maximum fluence of normal mucosa of small intestine was 4.9 Gy-Eq in pre-BNCT dosimetry. The tumour growth was regulated during 3 months by BNCT.

It is scheduled that the appropriate cases are enrolled in the future, and safety procedures and the therapeutic effects are examined in BNCT to locally recurred rectal cancers.

PI C2 01

Radiation-induced meningiomas after BNCT in patients with malignant glioma

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Introduction

It is well known that cranial irradiation may lead to tinea captis, neoplasm and vascular malformation as adverse effects. Radiation-induced meningiomas are the most common form of radiation-induced neoplasm reported in literature. It is known to occur after high- and low-dose cranial radiation therapy. Inclusion criteria for radiation-induced meningioma are reported as follows: 1) tumor must arise in the irradiated field. 2) histological feature must differ from those of any previous neoplasm. 3) a sufficient latency or induction period following radiation must elapse before meningioma is diagnosed. 4) no family history of pakomatosis. 5) tumor must not be recurrent or metastatic. 6) tumor must not be present prior to radiation therapy. The incidence of radiation-induced brain tumor has been reported as 1.37 %.

Material and Methods

The patient is 50-year-old male. He was diagnosed as anaplastic oligoastrocytoma (grade III) of right frontal lobe in 1987, and underwent intra-operative BNCT using BSH in 1988. Mean value of boron concentration in blood during BNCT was 26 ppm. Irradiation time was 320 min. Neutron flux and fluence at the brain surface was 1.0×10^8 n/cm².sec and 1.92×10^9 /cm², respectively. These at the target in the tumor was 4.0×10^7 cm².sec and 7.68×10^8 /cm², respectively. The calculated physical dose at target and vasculature was 14.8 Gy and 7.4 Gy, respectively. 1 year after BNCT, the patient was suffered from severe radiation

necrosis. Several times of necrotomy and ventriculo-peritoneal shunt were performed to reduce the condition of high intracranial pressure.

Result

After necrotomy, the clinical course was uneventful except of mild left hemiparesis. 16 years after BNCT, a follow-up MRI showed a left temporal convexity meningioma, which is contralateral side of the primary tumor, moreover, 22 years after BNCT left parasagittal meningioma was also recognized. Both tumors localized in the close site to irradiation field on BNCT. Gd-MRI demonstrated tumor growth in both, especially; left parasagittal meningioma demonstrated rapid growth. 27 years after BNCT, both tumors were removed totally. Left temporal convexity meningioma is very hard and well-demarcated, on the other hand, left parasagittal meningioma is soft and adhesin to surrounding brain tissue. Histopathological diagnosed was meningothelial meningioma (grade I) in both tumors.

Conclusion

Since 1968, we have treated 180 malignant brain tumors using BNCT. Only one patient (0.56 %) was suffered from radiation-induced meningioma 16 years after BNCT. It has been reported that radiation-induced meningioma tended to occur in high-dose (more than 20 Gy) irradiation, and in young patients. A long-term follow-up on MRI is necessary for long-survivors after BNCT in patients with malignant brain tumors.

PI C2 02

Glioma heterogeneity and the L-Amino acid transporter-1 (LAT1): A first step to stratified BPA-based BNCT?

D. Ngoga¹; C. L. Schütz²; A. Detta¹; S. Green²; G. Cruickshank¹

¹University of Birmingham, Queen Elizabeth Hospital, Department of Neurosurgery, ²University of Birmingham, Queen Elizabeth Hospital, Department of Medical Physics
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Recent findings from The Cancer Genome Atlas (TCGA) project have highlighted the highly heterogeneous nature of glioma and identified a number of distinct molecular subtypes. Though we are yet to fully understand their biological and clinical implications, genetic alterations such as IDH1 mutation, MGMT promoter methylation and 1p19q co-deletion have already proved to be of prognostic value and offer the opportunity of stratified treatments for patients with glioma. As BNCT emerges into routine clinical practice, an understanding of potential differences in treatment response by different molecular subgroups of glioma will be of increasing importance.

Boronphenylalanine (BPA), a well-studied compound in the context of BNCT is a substrate of the L-Amino-acid transporter 1 (LAT-1) which is highly expressed in a number of tumour types including glioma. Studies have suggested that expression of LAT1 is related to cellular uptake of BPA and therefore potentially response to BNCT. We sought to understanding how genetic and protein expression of LAT1 varies across the different molecular subtypes of low and high-grade glioma and how this impacts on patient survival.

We performed mutational and gene expression analysis to identify the four suggested molecular subtype of 58 patients with high and low grade glioma,

examining the extent to which the expression of LAT 1 varied across the glioma subtypes. Using the National Cancer Institute's Repository for molecular brain neoplasia data (REMBRANDT), We examined the effect of changes in gene expression and copy number alterations in the genes encoding the constituent protein elements of the LAT-1 transporter (SLC7A7, SLC7A5, and SLC3A2) on the survival of patients with low and high-grade glioma. Based on results of these studies we will discuss the potential role of LAT-1 in the stratification of BPA based BNCT and the implications for future clinical trials.

PI C2 03

Boron Neutron Capture Therapy (BNCT) in the Management of Recurrent Laryngeal Cancer

A. Haapaniemi^{1*}, L. Kankaanranta^{2*}, H. Koivunoro², K. Saarilahti², A. Mäkitie¹, T. Atula¹, H. Joensuu²

*Departments of ¹Otorhinolaryngology – Head and Neck Surgery and ²Oncology, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland.
email: aaro.haapaniemi@hus.fi*

Background

Salvage surgery is conventionally the only feasible treatment option for laryngeal cancer (LC) recurring after (chemo)radiotherapy ((C)RT). New organ sparing treatment modalities are needed to preserve the functioning larynx. Boron neutron capture therapy (BNCT) is a novel form of radiation therapy specially targeting tumor cells with minor effects to healthy tissues. BNCT can be safely administered to previously irradiated patients. Recently, a prospective non-randomized Phase I/II trial of BNCT in locally recurred head and neck cancer was published with encouraging results (Kankaanranta et al, Int J Radiat Oncol Biol Phys. 2012 Jan). The objective of this study was to evaluate the feasibility of BNCT as an organ sparing treatment modality for LC recurrence.

Patients and Methods

We present nine patients who received BNCT during 2005-2012 for recurrent LC. All patients had (C)RT as their primary treatment phase and three patients had undergone prior surgical treatment as well. In three patients, the disease was persistent after primary treatment. One patient received BNCT for an inoperable nodal recurrence and one for an inoperable tracheostomal recurrence. The other seven patients with a local recurrence were considered to have a feasible surgical treatment option as well. BNCT was given as a single session treatment or given twice at one to two month intervals. All patients received the boron carrier agent boronophenylalanine-fructose (BPA-f) 400mg/kg infusion in two hours followed by one-field or two-field neutron irradiation. After BNCT the patients were followed up at the Departments of Oncology and Otolaryngology at one to three month intervals.

Results

Six patients received a single BNCT and three patients received two successive BNCT treatments. All patients tolerated the treatment well and there were no major complications. The most common adverse effects were transient mucositis, oral pain and fatigue. Initial complete response was achieved in four patients, partial response in one patient and the disease was stabilized in four patients. Three patients later underwent total laryngectomy and two of them experienced delayed surgical wound healing and pharyngocutaneous fistulae. One patient

with initial complete response is alive and disease-free with a functioning larynx 43 months after treatment.

Conclusion

BNCT may add a non-surgical treatment option to the management of recurrent or inoperable LC. Although initial complete responses were observed, long-term laryngeal preservation was infrequent in the present patient series.

PI C2 04

Boron Neutron Capture Therapy for Locally Recurrent Head and Neck Cancer –A Review of Literature and A Comparison against Systemic Therapy

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Introduction

Patients with Locally Recurrent Head and Neck Cancer (LRHNC) are mostly treated with best supportive care or palliative chemotherapy, both with dismal results. 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. We present our study with an aim to firstly, assess the safety and efficacy of BNCT in the treatment of LRHNC patients; and secondly, to compare BNCT against the standard treatment of platinum-based chemotherapy.

Materials and Methods

BNCT studies of patients with LRHNC were identified using a search through PUBMED databases. In addition, we compared a BNCT study against a phase III trial where similar patients were treated with platinum-based chemotherapy only (CTX) in the reference arm and platinum-based chemotherapy plus Cetuximab (CTX/C225) in the experimental arm.

Results

7 studies of BNCT were found. The response rate ranged from 61 % to 100 %. BNCT is associated with median overall survival of 13 months, comparable to CTX/C225 (10.1months) and superior to CTX (7.4 months). The proportion of patients who experienced WHO grade 4-5 acute adverse events for BNCT, CTX/C225 and CTX were 3 %, 32 % and 34 % respectively.

Conclusion

Compared to the current best systemic therapy, BNCT is probably just as efficacious and with lesser side effects, allowing patients weeks to months of good-quality life, which might otherwise be spent undergoing protracted standard therapies. The widespread use of BNCT should be promoted.

PI C3 01

Glioma heterogeneity and the L-Amino acid transporter-1 (LAT1): A first step to stratified BPA-based BNCT?

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Recent findings from The Cancer Genome Atlas (TCGA) project have highlighted the highly heterogeneous nature of glioma and identified a number of distinct molecular subtypes. Though we are yet to fully understand their biological and clinical implications, genetic alterations such as IDH1 mutation, MGMT promoter methylation and 1p19q co-deletion have already proved to be of prognostic value and offer the opportunity of stratified treatments for patients with glioma. As BNCT emerges into routine clinical practice, an understanding of potential differences in treatment response by different molecular subgroups of glioma will be of increasing importance.

Boronphenylalanine (BPA), a well-studied compound in the context of BNCT is a substrate of the L-Amino-acid transporter 1 (LAT-1) which is highly expressed in a number of tumour types including glioma. Studies have suggested that expression of LAT1 is related to cellular uptake of BPA and therefore potentially response to BNCT. We sought to understand how genetic and protein expression of LAT1 varies across the different molecular subtypes of low and high-grade glioma and how this impacts on patient survival.

We performed mutational and gene expression analysis to identify the four suggested molecular subtype of 58 patients with high and low grade glioma, examining the extent to which the expression of LAT 1 varied across the glioma subtypes. Using the National Cancer Institute's Repository for molecular brain neoplasia data (REMBRANDT), We examined the effect of changes in gene expression and copy number alterations in the genes encoding the constituent protein elements of the LAT-1 transporter (SLC7A7, SLC7A5, and SLC3A2) on the survival of patients with low and high-grade glioma.

Based on results of these studies we will discuss the potential role of LAT-1 in the stratification of BPA based BNCT and the implications for future clinical trials.

PI C3 02

Application of BNCT to the treatment of HER2+ breast cancer recurrences: research and developments in CNEA

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Her2+ breast cancer subtype is characterized by overexpression of HER2 transmembrane protein in tumor cells. This overexpression is considered a poor prognostic factor associated to a lower disease-free survival and lower overall survival. According to statistical data published by the "National Program for Detection of HER2 Overexpression" in Argentina, the incidence of this breast cancer subtype is about 13 %. Currently, the development of targeted therapies allows for the treatment of this disease by combining chemotherapy and the administration of anti-her2 monoclonal antibodies known as Trastuzumab. However, many patients do not show a satisfactory response to this treatment.

A new research line has been started as part of the Argentine BNCT Project to address certain selected cases of those resilient her2+ breast cancers. Based on

former studies, this research considers the application of BNCT to the treatment of locoregional recurrences from her2+ breast cancer subtype. Nowadays, the essential concerns of this work are the development of carriers that improve the selectivity of delivery of boron compounds and the treatment feasibility assessment from dosimetric point of view. The development of the carriers considers the utilization of liposomes labeled with Trastuzumab which results in specific binding and internalization into HER2 overexpressing breast cancer cells. The proposed strategy would allow to enhance both selectivity and concentration levels of boron compounds in the tumor microenvironment.

The work being performed during this research involves the identification of a pool of specific clinical cases that could benefit from a potential application of the proposed treatment. The following locoregional recurrences of her2+ breast cancer have been found to be of interest: from local recurrence standpoint one can find the treated breast in the case of conserving therapy and the mastectomy bed in the case of mastectomy, and, from regional recurrence standpoint, one can find ganglionic regions such as axillary or supraclavicular ones. These cases are consequently taken into account in the computational dosimetric study, which is developed with the computational model of the upgraded RA-6 BNCT facility using MCNP codes and CT-based anthropomorphic voxelized computational models, to evaluate the boron biodistribution requirements that liposomes must fulfill.

About liposomes we have performed BPA encapsulation composed by POPC and PEG-DSPC lipids by two methodologies: film hydration and the reverse phase evaporation methods. Encapsulated boron was quantified by autoradiography and inductively coupled plasma (ICP) techniques achieving similar amounts with both methodologies of encapsulation.

Accordingly, initial considerations and discussions for and from the numerical dosimetric study and the current state of the boron carrier development will be presented for the proposed treatment.

PI C3 03

Pharmacokinetic analysis of Carotid BPA-Mannitol delivery in Human GBM indicates three compartment tumour uptake kinetics enhanced by specific LAT activity in the Brain around Tumour after resection.

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Analysis of the clinical data from the US (Brookhaven), Swedish (Studs vig), has been examined by Hopewell (2009) who concluded that the prolonged infusion program in Studsvig study was the major factor contributing to the differences in survival. A Phase I/II study including 30 patients in which the BPA-fructose dose was escalated in steps from 290 to 500 mg/Kg body weight, in all cases with a 2Hr infusion was reported by the Finnish team. The authors state that no association between BPA-f and duration and survival was evident in this small series, which

suggests also that simply increasing the dose without increasing the infusion time may not improve the therapeutic outcome. The simple two compartment model relating plasma concentrations to tumour levels is clearly inadequate to explain these findings.

In Birmingham we have tested a three compartment model based on our new understanding of the specific kinetics of the LAT1 transporter (Detta and Cruickshank 2009). We have performed pharmacokinetic (Pk) studies on a new formulation of BPA at ~100mg/ml (375mg/Kg in newly diagnosed glioma patients n= 10) which has been administered by central venous infusion and by close carotid infusion to allow a much higher plasma to brain ratio. The bioavailable impact of route of delivery, on brain parenchyma Boron levels also with a preinfusion mannitol blood brain barrier agent, has been determined by microdialysis and related to tumour concentration achieved. Tumour and Brain around tumour uptake varies in the kinetic pattern but suggests continuing uptake in BAT over time to over 30ppm.

This study confirms the safety and efficiency of this new formulation of BPA. This Pk Study indicates a high plasma to brain concentration gradient from carotid infusion and BBB manipulation, and reliably places Boron in high concentrations in the brain compartment. However the tumour uptake of Boron (BPA) is governed solely by the abundance and two way kinetics of LAT1. These manoeuvres allow short infusions, an early elevation of BPA in the brain compartment and the opportunity to optimize uptake for a given LAT1 expression, and may explain some of the variation in clinical results. Furthermore there is evidence that tumour remaining after surgery: the BAT population may have more predictable kinetics and a more favourable capacity to concentrate boron for BNCT therapy in our planned Phase 1 study.

PI C3 04

Biokinetic analysis of tissue ^{10}B concentrations of glioma patients treated with BNCT in Finland

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Introduction

In Finland, a total of 98 glioma patients, 59 with malignant glioma recurrence after surgery and 39 who had undergone surgery for newly diagnosed glioblastoma, were treated with L-BPA-F-mediated BNCT in 1999 to 2011. Normal-brain-to-blood (N/B) and tumor-to-blood (T/B) ^{10}B concentration ratios of 1 and 3.5, respectively, were assumed in dose calculations. A correlation between the calculated tumor doses and survival was not found, suggesting an incorrect estimation of the dose. In this study, the T/B and tumor-to-normal-brain (T/N) ratios are estimated using a closed 3-compartment pharmacokinetic model based on the measured blood ^{10}B concentrations.

Patients and Methods

Published average rate constants obtained from ⁸F-BPA-PET studies, and validated for a slow intravenous L-BPA-F infusion, were applied to predict the tumor and the normal brain ¹⁰B uptake based on the 3-compartment model and the measured blood ¹⁰B levels. Altogether 22 patients with recurrent glioma, treated within a clinical trial, were evaluated using their individual measured blood ¹⁰B concentration curves. The patients received a 290 to 450 mg/kg dose of L-BPA-F administered as a 2-hour intravenous infusion. Neutron irradiation was initiated 46 to 144 minutes after the end of infusion. The ¹⁰B concentrations of peripheral venous blood samples collected at 20-minute intervals were analyzed with inductively ICP-AES. The first blood sample was taken immediately before the initiation of the L-BPA F-infusion (the baseline sample), and the last one immediately after the completion of neutron irradiation.

Results and conclusions

According to the 3-compartment model, the T/B ratios reached their peaks of 2.3 to 3.1 at the time of the last blood sample taken after irradiation, consequently being lower during irradiation. The model predicts differing pharmacokinetics for the brain tissue and the blood, which results in distinct T/N and T/B concentration ratio curves. The highest T/N ratio of 1.9 to 2.0 was obtained at the end of the L-BPA-F infusion, and the ratio decreased thereafter gradually to 1.5 to 1.6. Instead of examining the T/N ratio, the ratio of tumor-to-combination of 1/3 blood + 2/3 the normal brain tissue $T/(1/3B+2/3N)$ has been proposed to be examined, as the vascular endothelium may be the main target of BNCT damage. The highest $T/(1/3B+2/3N)$ of 1.8 to 2.0 were observed 70 to 130 minutes after end of the L-BPA F-infusions, which was the time range within which all patients received neutron irradiation. The model suggests that the treated patients received a lower tumor dose than previously predicted due to considerably lower ¹⁰B levels in the tumor. The patient doses will be re-evaluated according to the ¹⁰B levels estimated here.

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Pa P1 01

Present Status of Accelerator-Based BNCT

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There is a strong international consensus that Accelerator-Based BNCT (AB-BNCT) may change the prospects of BNCT due mainly to the possibility of in-hospital siting in contrast to reactor-based facilities. Hence, there is a quest for finding the "best" technological solution for such a facility. Decision criteria may be: simplicity, safety and lowest possible cost in order to promote widest possible dissemination.

There are several high intensity accelerator-based facilities being constructed and tested worldwide. They will be compared according to the nuclear reaction employed, beam energy and current, target design and complexity, resulting primary neutron spectra features, resulting epithermal neutron beam characteristics, type of machine, cost, etc. Merits and demerits will be assessed.

In particular, the progress of the Argentine Electrostatic Quadrupole accelerator is described. A less-than-final-scale prototype is ready which has been shown to transmit proton beams of several mA. Beam diagnostics through fluorescence induced in the residual gas and emittance determinations will be presented.

At this point in time our attention is preferentially focused on the ${}^9\text{Be}(d,n){}^{10}\text{B}$ reaction and its suitability for AB-BNCT will be briefly mentioned. Progress in Be-based neutron production targets will also be briefly described.

In addition progress has been made in the design and optimization of a beam shaping assembly for near-threshold ${}^7\text{Li}(p,n){}^7\text{Be}$ -based AB-BNCT, a modality which also holds promise.

Pa P1 02

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

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A neutron irradiation system (NIS) for boron-neutron capture therapy (BNCT) can supply low-energy neutron irradiation field of less than several tens of keVs. The NIS for BNCT (BNCT-NIS) has two kinds, one is the Reactor based BNCT-NIS for neutrons from research reactors, and the other is the Accelerator based (Acc-based) BNCT-NIS. All nuclear reactors have similar characteristics of its neutron energy spectra because they are produced by the ${}^{235}\text{U}$ fission reaction during the critical state. They are capable of generating superior neutron intensity and temporal stability. Recently, progress in the Acc-based BNCT-NIS development has been achieved, because improved accelerator technology has overcome the neutron intensity shortage. The ${}^7\text{Li}(p,n){}^7\text{Be}$, ${}^9\text{Be}(p,n){}^9\text{B}$, ${}^9\text{Be}(p,xn)\text{X}$ reactions have become the viable candidates for neutron production. The characteristics of the produced neutrons, such as energy spectra and its angular dependence, varies for each reaction. Acc-based BNCT-NIS needs to satisfy not only the necessary conditions for BNCT irradiation, but also the stability required of a neutron source.

When the research and development of Acc-based BNCT-NIS approaches its practical implementation, the conditions and requirements related to BNCT should be carefully evaluated as much as possible. The main technical issues related to Acc-based BNCT-NIS are the heat removal of 30-80 kW and the radiation damage at the neutron producing target. Accordingly, high reliability of the neutron producing target which is brought about by the safety, stability and security of the system, is required for its clinical implementation. The Acc-based BNCT-NIS using neutrons from ${}^7\text{Li}(p,n){}^7\text{Be}$ was evaluated as a good combination with a liquid lithium target.

A stable liquid lithium film flow was established for use in the neutron producing target for BNCT. The combination of a long-life neutron producing target such as a liquid lithium target and a stable proton accelerator such as Radio Frequency Quadrupole (RFQ) is considered as a promising candidate for an Acc-based BNCT NIS. It was found that ${}^7\text{Li}(p,n){}^7\text{Be}$ near threshold reaction combined with a liquid lithium target is the most suitable neutron source for an Acc-based BNCT-NIS. And this system is also advantageous for the future system which is envisioned to have a non-invasive dose monitoring system during clinical BNCT.

Pa P1 03

Construction of Accelerator-based BNCT facility at Ibaraki Neutron Medical Research Center

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Abstract

An accelerator-based BNCT (Boron Neutron Capture Therapy) facility is being constructed at the Ibaraki Neutron Medical Research Center. It consists of a proton linac of 80kW beam power with 8 MeV energy and 10mA average current, a beryllium target, and a moderator system to provide an epi-thermal neutron flux enough for patient treatment. The technology choices for this present system were driven by the need to site the facility in a hospital and where low residual activity is essential. The maximum neutron energy produced from an 8 MeV-proton is 6 MeV, which is below the threshold energy of the main nuclear reactions which produce radioactive products. The down side of this technology choice is that it produces a high density heat load on the target so that cooling and hydrogen anti-blistering amelioration prevent sever challenges requiring successful R&D progress. The latest design of the target and moderator system shows that a flux of 4×10^9 epi-thermal neutrons / cm² / sec can be obtained. This is much higher than the flux from the existing nuclear reactor based BNCT facility at JAEA (JRR-4).

Pa P1 04

MUNES project: an intense Multidisciplinary Neutron Source for BNCT based on a high intensity RFQ accelerator

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At INFN LNL (Legnaro Italy) it has been built a high intensity Radio Frequency Quadrupole (RFQ), able to produce a 5 MeV proton beam of 30 mA. Coupled with a Be target such a beam can generate a neutron flux of 10^{14} n/s, with a spectrum centered in the MeV region (that has been recently characterized in detail at LNL accelerators). This neutron flux can be moderated to generate a thermal or epithermal source for BNCT with very little contamination of energetic form energetic neutron and gamma.

Since the approval of MUNES project (in 2012) the high technology issues related to a compact neutron source to be installed in an Hospital environment have been faced, specific accelerator elements have been prototyped and produced.

The main components of the accelerator of MUNES are the high current source of ECR kind, the RF accelerator of RFQ kind, able to operate in continuous wave mode, and the transfer lines with associated beam diagnostics. This approach is the same used for the injectors of the most powerful neutron sources proposed for the test of the structural material of future nuclear fusion reactors (IFMIF), or for the transmutation of nuclear wastes. Respect to other accelerators used for BNCT one can count on a very intense beam that will impinge on the water cooled beryllium target, and consequently on an intense neutron flux with low high energy neutron contaminants.

Part of the challenges of the accelerator, like mastering the beam space charge and power density with proper procedure and fast computer control systems, are common to the other applications (in which the same team is involved). But other challenges are specific of BNCT, and are those related to the use of such a powerful accelerator in a hospital or in a medical research center. For example, the powering of the accelerating structure (1 MW at 352 MHz) is an innovative system, completely based on solid state amplifiers. Respect to a conventional RF system based on klystron source this new RF source is easier and safer to be used outside Nuclear Physics lab.

A detailed outline of MUNES design choices and the status of the construction of the key components of the project will be given in the paper.

Pa P1 05

Analyzing the performance of accelerators in BNCT: evaluation of the therapeutic potential of the proposed facility and its comparison with global benchmark clinical beams

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Introduction

The aim of this work is to contribute to the development and optimization of accelerator based-Boron Neutron Capture Therapy (AB-BNCT) beam designs and the consolidation of this innovative treatment modality in the field of radiation therapy. This study is part of a broader program of the National Atomic Energy Commission of Argentina (CNEA) that includes the construction and installation of a particle accelerator of protons or deuterons of low energy (~ 2.3 or 1.5 MeV, respectively) and high current (~ 30 mA) for BNCT in a specialized cancer institute in Argentina. The capability of a beam shaping assembly (BSA) design developed for this accelerator to treat various disease sites was assessed in the clinical context of patient treatment plans, comparing its calculated performance with that obtained with existing high quality reactor-based neutron beams used in BNCT treatments.

Material and Methods

The first part of this work comprised the design of a new BSA based on previous work, together with the development of the methodology and software necessary for accelerator-based BNCT treatment planning. Well-characterized neutron beams from nuclear reactors used in the treatment of brain tumors (MIT FCB, USA and JRR-4, Japan) and cutaneous melanoma of the extremities (RA-6, Argentina) were used to assess the proposed design in a clinical scenario. We compared the quality of in-air beam parameters (flux, current, specific doses, etc.), both outside and inside the exit port. Also, dosimetric comparisons were made using clinical cases for two different disease sites: two glioblastoma multiforme cases involved in the clinical BNCT protocol of Harvard-MIT, and two nodular malignant melanoma cases treated with the B1 beam from the RA-6 reactor in the context of BNCT clinical studies in Argentina. In all cases, the comparisons were made under identical simulation conditions. To avoid introducing any bias, the definition of the calculated quantities (tallies), the composition of materials, voxel size, among others, were standardized. The NCTPlan treatment planning system and the MCNP5 transport code were used.

Results

Calculation of in-air parameters showed that the proposed accelerator beam design provides a neutron flux considered suitable for the therapy ($> 1.2 \times 10^9$ n/cm² s⁻¹, with 82 % in the epithermal energy range) with a relatively low contamination of fast neutrons and photons (specific doses of 5.5×10^{-13} and 2.9×10^{-13} Gy cm²/n, respectively). In addition, the radial neutron and gamma fluxes decline rapidly outside the exit port, thus yielding low peripheral dose. Simulating an analytical whole-body phantom confirmed the low peripheral doses, finding that mean doses computed in 15 organs are similar to those achieved with the epithermal beam mode of the JRR-4 reactor. Regarding the clinical cases, the calculated dose distribution to tumors and normal tissues are comparable to those obtained with the real beams considered in the study.

Conclusion

The international collaboration between the different BNCT clinical institutions allowed assessing the performance of an accelerator-based source design using existing neutron beams, the MIT FCB (USA), JRR-4 (Japan), RA-6 (Argentina) reactors, and treatment plans for real BNCT patients. In the intercomparison, in-air and in-patient figures of merit were considered. The calculations show that the proposed accelerator-based neutron beam yields good dosimetric performance, comparing favorably with existing epithermal neutron beams. Also, it has been

shown that an accelerator-based facility may be used in the treatment of both superficial and deep-seated tumors as long as different strategies for treatment planning are employed.

Pa B1 01

Evaluation of Carboranyl Thymidine Analogues as Potential Delivery Agents for Boron Neutron Capture Therapy

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Introduction

We have had a longstanding interest in carboranyl nucleosides as potential boron delivery agents for Neutron Capture Therapy (NCT). Among these are carboranyl thymidine analogues (CTAs), which are substrates for thymidine kinase-1 (TK1) and is only expressed in proliferating cells including a wide variety of malignant tumors. As has been previously reported by us, a panel of 3-carboranyl Thd analogues (3CTAs) have been designed and synthesized. One of these, designated N5-2OH, previously has been evaluated *in vivo* using two tumor model systems, the murine L929 tumor in nude mice to validate target specificity and the RG2 rat glioma in Fischer rats to evaluate its therapeutic efficacy. In the present report we describe additional studies with N5-2OH using the F98 rat glioma model.

Materials and Methods: Biodistribution and BNCT studies

The synthesis of the CTAs have been described in detail elsewhere. The F98 glioma, which was determined by Western blot to strongly express TK1, was used in order to assess the response to BNCT. This was carried out 14 d. after intracerebral (i.c.) stereotactic implantation of 10^3 glioma cells. One week before irradiation, the rats were shipped to MIT for irradiation at the MITR-II nuclear reactor. They were randomized into groups of 8-10 animals each as follows: (1) i.c. of N5-2OH over 24 hrs by Alzet pumps alone or (2) in combination with i.v. BPA; (3) i.v. BPA; (4) i.c. delivery of DMSO; and (5) unirradiated controls. Animals in Groups 1 and 2 received 500 μg of ^{10}B -enriched N5-2OH at the same concentration as that used in biodistribution studies. It contained 100 μg of boron, solubilized in 35 % DMSO in 200 μL , and was administered i.c. by Alzet[®] osmotic pumps over 24 h at a flow rate of 8.33 $\mu\text{L}/\text{h}$, after which BNCT was carried out. Animals in Groups 1 and 3 received 500 mg of ^{10}B -enriched BPA fructose i.v. 2.5 h prior to BNCT.

Results: Biodistribution studies and dosimetry

The tumor and normal brain boron concentrations were $17.3 \pm 4.3 \mu\text{g}/\text{g}$ and $< 0.5 \mu\text{g}/\text{g}$, respectively, and the blood values were undetectable ($< 0.5 \mu\text{g}/\text{g}$). The corresponding tumor and normal brain boron values for the combination at 1 h after termination of delivery of N5-2OH and 2.5 h following i.v. BPA were $28.0 \pm 4.5 \mu\text{g}/\text{g}$ and $4.0 \pm 1.3 \mu\text{g}/\text{g}$, respectively. In contrast, the tumor and normal brain boron values for BPA alone were $10.7 \pm 1.7 \mu\text{g}/\text{g}$ and $3.8 \pm 1.1 \mu\text{g}/\text{g}$, respectively. Based on these boron concentrations, the unweighted, absorbed physical radiation doses were 5.7 Gy for rats that received N5-2OH, 4.2 Gy for BPA alone, and 8.2 Gy for the combination.

Response to BNCT

The longest MST \pm standard error (SE) was 43.5 ± 5.9 d for animals that received N5-2OH and BPA vs. 37.9 ± 6.8 d for the rats that received N5-2OH alone and 36.7 ± 3.2 d. for those that received BPA alone. The MSTs of irradiated and untreated controls were 31.3 ± 3.9 d. and 25.4 ± 2.4 d., respectively. Neuropathologic examination of the brains of F98 glioma bearing rats all revealed invasive tumor.

Conclusions

The results from the present study are in contrast to those previously reported by us using the RG2 tumor models, which yielded more robust survival data. Equivalent MSTs were seen in animals that received either i.c. N5-2OH or i.v. BPA. The combination of both agents modestly increased the MST suggesting that the effect was additive. Additional studies have been carried out with two recently synthesized, water soluble CTAs, designated 18a and 18b, and these will be discussed in the oral presentation.

Pa B1 02

Dodecaborate clusters forms stable pores in lipid membranes

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The interaction of dodecaido dodecaborate clusters with lipid membranes was studied with different techniques. The zeta potential measurements show a strong interaction of the cluster with the liposomal surface. This interaction can induce the release of an encapsulated fluorophore already at very low concentrations of the cluster ($0.5 \mu\text{M}$), but depending on the salt solution used as buffer system. When heated in the presence of DPPC liposomes the dodecaido dodecaborate cluster shifts the main transition peak to lower temperatures and causes significant structural changes of the liposomal structure, as observed with cryo-TEM. The electrophysiological measurements show that the interaction of dodecaido dodecaborate clusters with black lipid membranes leads to transient holes in DPhPC lipid bilayers. These pores are as big as 45 \AA in diameter and open only shortly at higher cluster concentrations ($1 \mu\text{M}$), but at lower concentrations ($0.25 \mu\text{M}$) the pores are $10\text{-}17 \text{ \AA}$ in diameter and stable up to an hour. The pores open only under potential, but when the voltage is removed the pores are not closed, because when voltage is applied again the same amount of ion flow across the membrane is seen.

Leakage of liposomal content is also induced by BSH and other clusters, and morphological changes have been described before. We found recently that BSH can also induce stable holes in black lipid membranes.

These results can have bearing on the use of boron cluster compounds for BNCT.

Pa B1 03

Histamine reduces BNCT induced mucositis in precancerous tissue without affecting BPA biodistribution or long term inhibition of tumor development

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Introduction

The relatively poor overall 5-year survival rate for malignancies of the oral cavity poses the need for more effective and selective therapies. Studies in appropriate experimental models are pivotal to progress in this field. We previously evidenced the therapeutic efficacy of BNCT to treat oral cancer in an experimental model in the hamster cheek pouch. We also demonstrated a significant inhibitory long-term effect (8 months) of BNCT on the development of tumors in a novel model of oral precancer in the hamster cheek pouch. Despite therapeutic success, BNCT-induced mucositis in precancerous tissue was dose limiting and favored tumor development. In a clinical scenario, oral mucositis limits the dose delivered to head and neck tumors and affects patients' quality of life. Nowadays, oral mucositis continues to represent an important unmet medical need. The present study aims to evaluate the effect of radioprotective agents, seeking to reduce BNCT-induced mucositis to acceptable levels in precancerous tissue, without negative local or systemic side effects, and without affecting boron compound biodistribution or compromising BNCT therapeutic effect.

Materials and methods

The DMBA-cancerized pouch of 5 groups of hamsters was exposed to BPA-BNCT at 5 Gy mean absorbed dose at RA-3 and treated, 1 day before BNCT and daily for 15 days after BNCT with G1) histamine LOW concentration (n=6, 1 mg/kg, subcutaneously -sc-); G2) histamine HIGH concentration (n=6, 5 mg/kg, sc); G3) JNJ7777120 (n=5, 10 mg/kg, sc); G4) JNJ10191584 (n=3, 10 mg/kg, sc); G5) no radioprotective treatment (n=5-11). The animals were followed for 8 months. Histamine, JNJ7777120 and JNJ10191584 were previously proved to exert a radioprotective effect in other experimental models. We performed biodistribution studies in two groups of DMBA-cancerized animals: G1) BPA+histamine LOW concentration (n=4) and G2) BPA only (n=2).

Results and Conclusion

Histamine LOW concentration did not alter boron concentration from BPA in blood, precancerous or normal pouch tissue. Only reversible irritation was seen at the injection site for all the radioprotective protocols. Regarding mucositis, animals treated with BNCT only, BPA-BNCT+Histamine HIGH concentration, BPA-BNCT+JNJ10191584 and BPA-BNCT+JNJ7777120 exhibited a higher incidence of unacceptably severe mucositis than animals treated with BPA-BNCT+Histamine LOW concentration (55 %, 67 %, 100 %, 43 % versus 17 %). Finally, none of the protocols compromised the therapeutic effect of BNCT in terms of inhibition of tumor development from precancerous tissue at 8 months after treatment. This study would suggest the potential use of Histamine LOW concentration (1mg/kg) to reduce severe and unacceptable mucositis associated with BPA-BNCT at 5 Gy total dose.

Pa B1 04

Combined effect of e-LinAc high-energy radiotherapy treatment and BNCT on human cell lines

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Conventional high-energy (15 MV–25 MV) electron linear accelerators (e-LINACs) for radiotherapy produce fast secondary neutrons with a mean energy of about 1MeV due to (γ, n) reaction. Moreover, due to the moderating effect of human body, an unavoidable thermal neutron fluence rate (of about $1.55E07 n_{th} cm^{-2} per Gy$) is localized in the tumour area.

This study analyses the possibility to employ this thermal neutron background to enhance the radiotherapy treatment effectiveness, previously administering ¹⁰B-Phenyl-Alanyne (¹⁰BPA) to the patient: the thermal neutron peak could be exploited for BNCT (Boron Neutron Capture Therapy) applications, delivering an additional therapeutic dose to the photon dose concentrated in tumour cells, acting as a localized radio-sensitizer.

The anthropomorphic phantom Jimmy, designed and realized by INFN Sec. Turin in collaboration with the Ispra JRC (Join Research Center) has been exposed to the Elekta Precise 18 MV photon beam, simulating a prostate radiotherapy treatment. By means of BDT and BD-PND bubble dosimeters placed at different depths inside the phantom, in holes corresponding to critical organs according to ICRP 60 recommendations, thermal and fast neutron dose respectively have been measured during the treatment. The experimental results are in good agreement with the simulation data obtained by MCNP4B-GN Monte Carlo simulation code. From this investigation it is evident that a consistent fluence rate of thermal neutrons, useful for BNCT, is concentrated in the target volume, while lower intensity neutron flux affects nearby organs (outside the treatment zone). The value of BNCT weighted biological dose, evaluated by MCNP4B-GN code, varies on the base of collimation techniques and MU (Monitor Unit) number as well as the target volume position (in the order of about 40 mGy-eq/Gy).

Moreover a biological study has been carried out exposing to e-LINAC photon beam cell lines of human lung adenocarcinoma, with and without BPA administration, inserted at 4 cm depth in cubic simplified polyethylene phantom; the survival curves have been analyzed after irradiation, and an 30 % increase of apoptosis in cells treated with BPA has been measured, confirming the synergy between high-energy photon therapy and BNCT effect. These results suggest that the thermal neutrons produced inside the human body during a traditional high-energy radiotherapy treatment, could be employed to enhance selectively the administered therapeutic dose.

Pa B1 05

Comparative Study of the Radiobiological Effects Induced on Adherent vs Suspended Cells by BNCT, Neutrons and Gamma Rays Treatments

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Introduction

Extensive preclinical *in vitro* studies are mandatory in order to assess the applicability and efficacy of Boron Neutron Capture Therapy (BNCT) to any neoplasia of interest. The present study is part of the experimental preclinical validations aimed to verify the applicability of BNCT to liver and lung coloncarcinoma metastases and to limb osteosarcoma. The biological effects induced by radiation treatments, such as the reduction of the proliferative capacity and the delay in the cell cycle progression, were evaluated on cells exposed to Cobalt-60 γ -rays (⁶⁰Co) and to neutron irradiation. Neutron treatment was performed both on cells previously loaded with boron and on unloaded ones. Since cells can be irradiated as adherent or after their detachment from the culture flask, as cell suspensions, aim of these study is to investigate if this two different modalities of cell exposure to radiations influence their radiosensitivity.

Material and Methods

Experiments were performed on the rat coloncarcinoma, DHDK12TRb and osteosarcoma, UMR-106 cell lines that grow as confluent monolayer. Cell survival was assessed by the plating assay test while cell cycle was evaluated by the cytofluorimetric DNA analysis performed after propidium iodide counterstained cells.

For ⁶⁰Co irradiation of cell suspensions, subconfluent cells were trypsinized, counted, transferred into polythene tubes and housed in a special Plexiglas stand for the subsequent irradiation at 3.5, 5, 7 and 10 Gy in electronic equilibrium conditions. Immediately after irradiation, for DNA profile studies, cells were reseeded into two flasks, for each of the following days of observation (1, 2, 5 and 7 days), while for plating assay, after suitable dilutions, cells were seeded into Petri dishes and allowed to grow until discrete colonies formation. ⁶⁰Co irradiation of adherent cells was performed directly in the culture flasks containing the culture medium, in electronic equilibrium conditions. After irradiation cells were suspended by trypsin, counted and seeded as previously described into flasks or Petri dishes. For neutron irradiation of suspensions, cells untreated and treated for 4 hours with 80 μ g/ml Boronophenilalanine (BPA), were exposed to the neutron flux in polythene tubes housed in a Teflon stand; adherent cells were submitted to neutrons in the culture flasks, by replacing the medium in case of BPA treated samples. In both cases the absorbed dose range was 0.1Gy – 12 Gy. At the end of irradiation, cells were processed as described for ⁶⁰Co irradiation.

Results and Conclusions

The present study evidences that adherent cells are much more radiosensitive to both low and high LET radiations than suspended cells. The enhanced block of the cell cycle progression in G₂ phase, observed in suspended with respect to adherent cells, suggests the presence of an higher repair capability. The modality of cell exposure to irradiation must therefore be considered as an additional factor influencing cell survival to radiation treatments and as a variable to be taken into account in comparing intra and inter laboratory radiation survival results, also in case of BNCT treatment.

Pa Ch1 01

Direct Synthesis of Boron-containing Ugi Analogues and their Biological EvaluationsRu-Ching, Lian¹, Meng-Hsuan Lin¹, Jia-Jie Fu¹, Meng-Ju Wu¹, Yang-Chang Wu², Fang-Rong Chang³, Po-Shen Pan¹

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A four-component Ugi reaction (Ugi-4CR) utilizing formylphenyl boronic acid under mild conditions was developed for the synthesis of boronic acid analogs. The reactions were performed in methanol and accelerated by microwave irradiation, which makes this strategy well suited for constructing boron-containing chemical libraries. Two of the synthesized analogs were found to have potent activity against HepG2, MDA-MB231, and A549 cancer cell lines, demonstrating the potential application of this approach in developing novel boron-containing pharmaceuticals.

Pa Ch1 02

Development of Albumin-bound *closo*-Dodecaborate and its Promising Boron Delivery Efficacy to TumorDaisuke Kanoh,¹ Shoji Tachikawa,^{1,2} Shinich Sato,² Hirovuki Nakamura^{*1,2}

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Albumin, a major plasma protein constituent, is composed approximately 55 % of the human plasma protein. Albumin has been extensively investigated as a versatile carrier for therapeutic and diagnostic agents, including diabetes, cancer, rheumatoid arthritis and infectious diseases. For example, Abraxane[®], an albumin-paclitaxel nanoparticle, is the most advanced drug delivery product first approved by FDA in 2005 for the treatment of metastatic breast cancer. Furthermore, albumin microspheres have been investigated in controlled release systems as vehicles for delivery of therapeutic agents to local sites.

We focused on bovine serum albumin (BSA) as a boron carrier and studied conjugation of *closo*-dodecaborates to BSA. We chose a maleimide as a functional group to conjugate with BSA and designed a maleimide containing *closo*-dodecaborate (MID). It is known that a maleimide readily reacts with free sulfhydryl groups to form a covalent, thus it has been widely used for protein modification with small molecules at the cysteine residue. In this paper, we report design and synthesis of MID and the preparation of MID-BSA conjugates as new boron delivery vehicles for boron neutron capture therapy.

We synthesized MID from *closo*-dodecaborate-1,4-dioxane complex developed by Bregadze and coworkers. Tetrabutylammonium *closo*-dodecaborate was treated with 1,4-dioxane in the presence of NaBF₄ and HCl to give *closo*-dodecaborate-1,4-dioxane complex, which underwent a ring opening reaction with tetrabutylammonium azide in dichloromethane. The resulting *closo*-

dodecaborate conjugated azide was converted to aminoethoxyethoxy-*closo*-dodecaborate by Staudinger reaction, and then treated with 4-maleimidobutyric acid under the amide bond forming reaction condition to afford a tetrabutylammonium salt of MID. Finally, the tetrabutylammonium salt was converted to the sodium salt of MID for use in further biological experiments.

We first examined cell viability of MID using colon 26 cells and observed that MID showed a quite low cytotoxicity with a concentration to inhibit 50% cell growth (GI50) of higher than 1 mM. We next examined conjugation of MID to BSA. The reaction was carried out in a buffer (pH 7.4) at room temperature for 1 h. The conjugation was confirmed by western blotting analysis using anti-BSA antibody, which was kindly donated by Professor M. Kirihaata (Osaka Prefecture University), and MALDI-TOF MS analysis after trypsin digestion. BSA-bound *closo*-dodecaborates obtained from the above reaction was accumulated in colon 26 cells in a concentration-dependent manner. Interestingly, higher boron accumulation was observed in the cells incubated in the absence of BSA in the medium, revealing that BSA in the medium competitively inhibits the uptake of the BSA-bound *closo*-dodecaborates by colon 26 cells. The *in vivo* biodistribution experiment showed that the BSA-bound *closo*-dodecaborates were highly accumulated in tumor and their delivery efficacy was much higher than that of boron liposomes that were developed in our group. The detailed observations will be presented.

Pa Ch1 03

Gadolinium Neutron Capture Therapy Agents Targeting Mitochondria

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The 157-gadolinium (¹⁵⁷Gd) isotope (2.55 x 10⁵ barns, 15.7 % natural abundance) exhibits a 66-times greater probability of capturing thermal neutrons compared to the 10-boron nuclide, and thus it should be considered for future clinical NCT studies. However, the lack of suitable GdNCT agents for therapeutic applications is a key issue. Since the key ionizing radiation (Auger and Coster-Kronig electron) produced during the neutron capture process is limited to molecular (nm) dimensions, it is essential the Gd atoms are located in proximity to relevant sub-cellular components (e.g. DNA or mitochondria). GdNCT is especially relevant when considering healthy brain tissue as important structures may be located closely to the site of malignancy.

This work will highlight important biological studies underlying the localisation of a new class of tumor-cell specific GdNCT agents within mitochondria which can exploit the large difference in mitochondrial membrane potential between healthy and tumor cells. Experiments were carried out using highly water-soluble, non-cytotoxic (IC₅₀ > 1 mM) and highly tumor cell-selective GdNCT agents based upon phosphonium salts, with a tumor cell/healthy cell ratio > 6/1. In all studies, both human GBM (T98G) cells and normal, human glial (SVG p12) cells were used. The biological assays that were conducted include a determination of *in vitro* cytotoxicity, cellular uptake of Gd, tumor selectivity ratio, apoptotic profile and mitochondrial O₂ consumption rate profile using selected Gd(III) complexes. The results presented will showcase the great potential of these Gd agents which

have been specifically designed for NCT and related binary therapies such as photon activation therapy (PAT).

Pa Ch1 04

***In vivo* evaluation of Gd-DTPA-incorporated calcium phosphate nanoparticles for neutron capture therapy agent**

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The use of gadolinium as neutron capture therapy (NCT) agent has been getting attention because of its highest thermal neutron cross section (255 000 barns), which is around 65 times higher compared to commonly used boron in NCT. Gadolinium neutron capture reaction (Gd-NCR) also produces secondary particles with total kinetic energy about 3 times of that produced by boron in boron neutron capture therapy (BNCT). ¹⁰B isotope used in BNCT undergoes the reaction ¹⁰B(n,α)⁷Li with products of high linear energy transfer particles, alpha particles and lithium ions, where the combined path length is approximately one cell diameter i.e. about 12 microns. This theoretically limits the radiation effect to those tumor cells that have taken up a sufficient amount of ¹⁰B. On the contrary, this short flight range of alpha particles and lithium ions is actually making an inherent problem that it is necessary to deposit boron intracellularly to destroy the cell. In contrast to boron-neutron capture, Gd-NCR also results in release of gamma rays followed by a series of high linear energy transfer internal conversion and Auger electrons. Emitted gamma ray from Gd-NCR makes it a favorable characteristic because the location of the element is not critical with regard to target cell due to their longer flight ranges. Another advantage of Gd-NCT is that several gadolinium-based compounds are already approved in clinical as MRI contrast agent, which makes it possible to integrate radiotherapy and MRI diagnosis for visible cancer therapy.

The concept of Gd-NCT was first formulated in the 1980s as an alternative to ¹⁰B, but its development has been limited due to lack of appropriate gadolinium containing tumor-selective agents. In our previous study, we have evaluated gadoteridol-entrapped liposome as NCT agent by performing *in vivo* experiment on colon-26 tumor-bearing mice, and the results had shown significant tumor growth suppression after neutron irradiation, which proves the effectivity of the treatment. This has given the motivation to evaluate another gadolinium based compound as NCT agents. P. Mi et al., have developed PEGylated calcium phosphate nanoparticles incorporating Gd-DTPA (Gd-DTPA/CaP) from hydrothermal treatment, and it could selectively enhance the contrast in tumor positions for cancer diagnosis by MRI. Calcium phosphate-based nanoparticles has the characteristic of adequate biodegradation and excellent biocompatibility, which makes it attractive candidates for drug delivery application. The hydrothermal treated Gd-DTPA/CaP has also been proven to retain high stability

in physiological condition and has been indicated that the blood circulation time was remarkably extended compared to free Gd-DTPA. Herein, we performed *in vivo* evaluation of Gd-DTPA/CaP for further investigation of this compound as a feasible Gd-NCT agent.

PI B1 01

From Translational BNCT Studies in Animals to Clinical Trials

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In this presentation I will describe how studies carried out using experimental animal tumor models have advanced the clinical application of BNCT. The *first* were studies carried out by Albert Soloway and Hiroshi Hatanaka at the Massachusetts General Hospital, Boston, MA in the 1960's to develop boron delivery agents that would be more tumor selective than the boric acid derivatives, which had been used clinically by Sweet et al. in the 1950's. These initial studies were followed by extensive animal studies by Hatanaka, upon his return to Teikyo University in Tokyo, Japan, with sodium undercahydro-*closo*-dodecaborate (sodium borocaptate or BSH) which was the most promising of the compounds synthesized by Soloway et al.

This led to the first clinical trial in patients with brain tumors beginning in 1968. In the 1980's BSH was the only boron delivery agent used for the treatment of patients with a variety of brain tumors until the *second* major advance can be credited to Yutaka Mishima and his co-workers at Kobe University in Japan. Mishima, a dermatologist who had a special interest in melanoma, focused his attention on low molecular weight, boron containing compounds that might enter into the biosynthetic pathway for melanogenesis. After extensive animal experiments in melanoma bearing Syrian hamsters and Duroc pigs, Mishima concluded that p-boronophenylalanine (BPA) would be a suitable boron delivery agent for the treatment of patients with cutaneous melanomas. In a landmark paper (Lancet, 1989) he described the successful treatment of a patient with a primary cutaneous acral melanoma by the peritumoral administration of BPA and this was followed by the treatment of patients with cutaneous melanomas over various parts of the body and melanoma metastatic to lymph nodes.

The *third* major advance attributable to studies carried out in experimental animals was the report of Jeffrey Coderre and his co-workers at the Brookhaven National Laboratory in New York. They observed that BPA could be used to successfully treat and even cure Fischer rats bearing intracerebral (i.c.) implants of the 9L gliosarcoma. This was followed by Barth and his research team who reported that BPA also could be used to treat and even cure rats bearing the highly invasive F98 rat glioma, as well as rats bearing i.c. implants of the human MRA 27 melanoma as a model of melanoma metastatic to the brain. Based on these and other experimental animal studies, clinical biodistribution studies of BPA were initiated by several groups in patients with high grade gliomas and this was followed by the first of a number of clinical trials, including patients with recurrent therapeutically refractory head and neck cancer.

Fourth, based on studies of Barth and his research team at The Ohio State University and Ono and his co-workers at the Kyoto University in Japan the combination of BSH and BPA was evaluated to treat either F98 glioma bearing rats or SCC VII tumor bearing mice. These studies demonstrated the superiority of using BPA and BSH in combination and laid the groundwork for clinical studies

by Miyatake and Kawabata and their colleagues at Osaka Medical University.

Fifth, and last, Barth, using the F98 glioma, and Ono, using the SCC VII tumor model, demonstrated that a significant therapeutic gain could be obtained combining BNCT with a photon boost. This also was quickly translated into clinical use by Miyatake and Kawabata and their co-workers. All of the clinical advances in BNCT enumerated above were directly dependent upon animal studies and there is every reason to believe that such translational studies will continue to play an important role in the future development of BNCT.

PI B1 02

BNCT in an experimental model of lung metastases in BDIX rats

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Introduction

BNCT has been proposed for the treatment of non resectable, diffuse tumors in lung. The lung is the most frequent (and sometimes unique) site of metastases for several tumor types. Surgical resection is not an option when metastases are multiple, and chemotherapy is often ineffective. In these cases the short-term mortality rate is 100 %. The aim of the present study was to perform BNCT studies in an experimental model of lung metastases to assess therapeutic efficacy and potential toxicity.

Materials and Methods

3 x 10⁶ colon carcinoma cells (DHD/K12/TRb) in 0,5 ml of medium were injected *iv* in syngeneic BDIX rats. Three weeks post-inoculation, the rats had developed diffuse tumors in lung and were used for *in vivo* BNCT studies at RA-3. Based on previous biodistribution studies and employing computational dosimetry with Monte Carlo simulation, we prescribed 2 different doses, i.e. minimum absorbed dose to tumor 4 Gy (low dose, **LD**) and 8 Gy (high dose, **HD**). The animals were divided into 5 experimental groups for each dose level experiment: **T0** (euthanasia pre-treatment), **BPA-BNCT**, **(BPA+GB-10)-BNCT**, **Beam only** (background dose) and **Sham** (same manipulation, no treatment). The animals were followed clinically and euthanized 2 weeks after irradiation to assess tumor response and potential toxicity in normal lung, both at macroscopic and histological levels. To date, we have used the parameter % lung mass/body mass as an end-point to evaluate tumor response (tumor growth in lung is correlated with lung mass). An additional group of normal animals were euthanized to assess normal lung mass (no tumor growth).

Results

The statistical analysis (ANOVA) of the % lung mass/body mass showed statistically significant differences ($p < 0.05$) between **T0** ($0.73 \pm 0.34\%$, $n=13$) and **Sham** ($1.58 \pm 0.95\%$, $n=18$) indicating that, left untreated, animals exhibited significant tumor growth over the 2-week period that elapsed between

euthanasia of **T0** animals and **Sham** animals. No significant differences were observed between **Sham** and **Beam Only** at both dose levels (**LD**: $1.48 \pm 0.64\%$, $n=5$; **HD**: $1.58 \pm 1.24\%$, $n=9$). Tumor response for **BPA-BNCT (LD and HD)** and **(BPA+GB-10)-BNCT (HD)** was significant vs. **Sham**. No statistically significant differences in tumor response were observed between both dose levels, i.e. **BPA-BNCT (LD)** ($0.56 \pm 0.11\%$, $n=5$), **BPA-BNCT (HD)** ($0.69 \pm 0.20\%$, $n=8$) and **(BPA+GB-10)-BNCT (LD)** ($0.75 \pm 0.30\%$, $n=5$), **(BPA+GB-10)-BNCT (HD)** ($0.64 \pm 0.23\%$, $n=7$). The BNCT groups did not exhibit significant differences with T0, revealing that BNCT halted tumor growth. No clinical, macroscopic or histological changes were observed in normal lung in any of the groups.

Conclusion

BNCT induced a partial, consistent and significant control of lung metastases, 2 weeks post-irradiation, with no associated toxicity.

PI B1 03

Boron neutron capture therapy as new treatment for clear cell sarcoma: Trial on a lung metastasis model of clear cell sarcoma

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Introduction

Clear cell sarcoma (CCS) is a rare malignant tumor with a poor prognosis. Metastasis occurs in more than 50 % of such patients. Lung is common sites of metastasis. Although the standard treatment for CCS is wide surgical resection, there are no effective treatment methods for lung metastasis. Our previous study demonstrated that CCS has the ability to highly take up ¹⁰B with the use of *p*-borono-L-phenylalanine (L-BPA) *in vitro* and *in vivo*. As a result, disappearance of the tumor could be achieved after BNCT was carried out for subcutaneously CCS-bearing mice. In the present study, we established a lung metastasis model of CCS and investigated *in vivo* biodistribution of L-BPA and antitumor effect after BNCT in the lung metastasis model.

Materials and Methods

MP-CCS-SY, a CCS cell line of human origin, was suspended in 10 µg Matrigel[®], injected into a parenchyma of left lung in 7 weeks-old female nude mice. After 8

weeks, a tumor mass was observed in lung of the mice by a CT scan. BPA-Fr (24 mg ¹⁰B/kg) was intravenously administered to the lung metastasis model of CCS. At a predetermined time after administration, the mice were sacrificed and blood and tissue samples were collected immediately. In BNCT trial, the lung metastasis model of CCS was divided into BNCT group and control group (n=4). The thermal neutron was irradiated to the whole lung at KURRI.

Results

The lung metastasis model of CCS was obtained successfully; the tumor mass was found to be localized in surface of left lung parenchyma of the mice by macroscopic observation and the CT scan. One hour after the BPA-Fr administration, ¹⁰B concentration in tumor tissue in the lung metastasis model reached 51 μg ¹⁰B/g wet tumor tissue. Tumor-to-blood and tumor-to-normal tissue (left lung) ratios were 5.3 and 11.8, respectively, at the same time point. In BNCT trial, the growth of tumor mass was observed in control group. In contrast, BNCT group showed a significantly suppressed tumor-growth with no damage of normal lung.

Conclusion

The results indicate that BNCT with the use of BPA-Fr can be a promising therapeutic option for the lung metastasis of CCS.

PI B1 04

First results of pre-clinical studies of BNCT for Osteosarcoma

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Introduction

BNCT application is being investigated for limb osteosarcoma (OS) in Pavia, Italy. This tumour is characterized by an infiltrative nature that makes difficult its surgical removal without positive margins. OS is a radio-resistant tumour with a high probability of local recurrence or lung metastases and it usually affects a young population. BNCT could be an option as adjuvant therapy thanks to its selectivity in targeting tumour cells infiltrated in normal tissue and to the biological effectiveness of the high LET radiation. Pre-clinical studies are meant to verify ¹⁰B selective uptake in a rat model of OS treated with BPA. The effectiveness of BNCT for OS is assessed by animal irradiation in the thermal column of the TRIGA reactor of Pavia University. Finally, treatment planning simulations have been performed in order to establish the optimal characteristics of the neutron beam to be employed for patients.

Materials and Methods

Sprague-Dawley rats were inoculated with UMR-106 cells to generate limb OS as described in [Ferrari et al., ARI, **67**, 2009, S341–S344]. Two BPA administration routes were employed: intra-peritoneal and local intra-muscular injection. The animals were sacrificed 4 hours after administration and healthy muscle and OS were taken for boron measurements by neutron autoradiography and alpha spectrometry. As the methods to analyze hard tissues such as bone is still under development (see Provenzano et al., this congress), the muscle surrounding the tumour was taken as the reference value for the healthy tissues. OS developed in animals could be sectioned as a soft tissue.

Animals treated with BPA were irradiated in the thermal column of the TRIGA reactor, inside a neutron shield that exposed only the limb, in a position where the thermal neutron flux in air is $1.2 \cdot 10^{10}$ n/cm² s. Healthy animals and animals with OS were irradiated 4 hours after BPA administration, testing both local and intra-peritoneal administration. A group of animals were irradiated without BPA and another group served as control for tumour growth evaluation.

CT scan of a patient affected by limb OS was employed for treatment planning simulations by NCTPlan and MCNP5. Different ideal beams were tested from the point of view of dose distributions, with energy ranging from thermal to epithermal in a one-beam configuration. Realistic neutron spectra from nuclear reactor and accelerators were also tested in order to determine the most suitable realistic beam to treat OS. Boron concentration in muscle and in OS was set as measured in rats and other tissues were assumed to uptake typical boron concentration.

Results

Boron concentration measurements show high variability between animals even within the same protocol. On average, intra-peritoneal BPA administration shows a higher uptake both in healthy muscle (between 15 and 20 ppm) and in tumour (between 30 and 60 ppm) in comparison to the other protocol, and the ratio of boron concentration ranges from 2 to 4. Local administration shows poorer selectivity, the healthy muscle and the tumour taking-up around 10 ppm.

The shield was proven to be suitable for irradiation in the thermal column of the TRIGA reactor, allowing to protect the body and to preserve the animals from adverse irradiation effects. Tumour growth evaluation and normal tissues effects are under evaluation and will be presented.

The treatment plan simulations employing the CT scan of patient show that it is possible to obtain a favorable dose distribution in tumour without exceeding the tolerance limits for skin and for the other tissues involved in the irradiation.

PI B1 04

Examination of the usefulness as the new boron compound of ACBC-BSH

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Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when non-radioactive ¹⁰B is irradiated with low energy thermal neutrons to produce α - particles (¹⁰B[n, α]7Li). The L-amino acid transport system in tumor cells is enhanced compared with normal cells. Thus, Boron-containing α -amino acids showed intense uptake in the tumor cell. In particular, 1-amino-3-fluorocyclobutane-1-carboxylic acid (ACBC), unnatural amino acid was reported as the agent which showed intense uptake in glioblastoma. Additionally, in a clinical study, [¹⁸F] ACBC showed usefulness for tracer of positron emission tomography (PET). Therefore, we designed and synthesized ACBC-BSH. The goals of this study were two-fold. *First*, to determine the biodistribution of ACBC-BSH following intracerebral (i.c.) administration by means of short term (30 min) convection enhanced delivery (CED) or sustained delivery over 24 h by osmotic pumps to F98 glioma bearing rats.

Second, to determine the efficacy of ACBC-BSH as boron delivery agents for BNCT in F98 glioma bearing rats. Tumor boron concentrations 1 h after i.c. osmotic pump delivery were high (21.1 μ g/g). The corresponding normal brain concentrations were low (1.5 μ g/g). Based on these data, therapy studies were initiated at the Nuclear Reactor Laboratory at Kyoto University Research Reactor Institute (KURRI) with ACBC-BSH after osmotic pump delivery. Mean survival times (MST) of untreated and irradiated control rats were 27.2 \pm 2.4 and 29.8 \pm 1.9 d, respectively, while animals that received ACBC-BSH, followed by BNCT, had a MST of 37.0 \pm 5.2 d respectively, which were similar to those obtained following i.v. administration of boronophenylalanine (BPA) (37.4 \pm 2.6 d). And ACBC-BSH after osmotic pump delivery+ i.v. BPA had a MST of 44.3 \pm 8.0 d. The tumor boron concentrations of the ACBC-BSH (21.1 μ g/g) were similar to i.v. BPA (19.7 μ g/g) and immunostaining of F98 cells showed that BPA was widely distributed in the cytoplasm and cell nuclei and ACBC-BSH was incorporated into the cell membrane of the F98 cells and aggregated on the fringe of the cell nuclei, therefore we had expected that the ACBC-BSH MSTs would have been greater. But the curative effect of both was approximately equal. The reason is that I think that extracellular accumulations of ACBC-BSH indicating that the seemingly high tumor boron concentrations did not represent the true tumor cellular uptake. And we did not compete for the curative effect by using ACBC-BSH together in BPA and accepted meaningful duration of survival time. Difference in drug distribution at the cell level was regarded as the cause. This study suggested the possibility that ACBC-BSH became the drug to add curative effect to.

PI Ch1 01

Boron clusters as boron carriers for BNCT: Possibilities and problems

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Boron clusters have been used quite extensively to deliver boron to tumors. The chemistry of modification is reasonable well established, and numerous attempts of synthesis and testing of cluster-containing tumor seekers are found in the literature.

Recent publications point to potential problems in the use of boron clusters. Cluster compounds have been found to interact with proteins (notably enzymes), and specific compounds have been designed as enzyme inhibitors or receptor antagonists or agonists. For some compound classes, toxicity and unwanted side effects are observed when the compounds are administered in concentrations necessary for BNCT.

Some of these problems might have to do with the unusual way how boron clusters interact with other, organic material, such as proteins, sugars, and lipids, and how they are hydrated. These interactions will be reviewed for the different classes of clusters.

PI Ch1 02

High Mitochondrial Accumulation of New Gadolinium Agents Within Tumor Cells For Binary Cancer Therapies

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In Gd neutron capture therapy (NCT), the Auger Coster-Krönig (ACK) electrons represent the main therapeutic entity derived from the thermal neutron capture reactions of the naturally-occurring, non-radioactive ¹⁵⁷Gd isotope (natural abundance = 15.7 %), which possesses the highest neutron-capture cross-section of all stable nuclides (2.55 x 10⁵ barns). In photon activation therapy (PAT), emission of ACK electrons from high-Z atoms can also be achieved by means of X-ray photons due to the photoelectric effect and, unlike NCT, is independent of isotope. Thus, two related binary therapies for the treatment of aggressive and intractable cancers such as GBM can be considered for this particular lanthanide element. One critical aspect of both NCT and PAT is the development of tumour-selective agents which can localize in high quantities (> 100 ppm) near important sub-cellular components and can lead to a therapeutic effect upon thermal neutron or X-ray photon irradiation, respectively. The macrocyclic texaphyrin derivative known as Motexafin-Gd (MGd, Xcytrin[®]) is to date the only clinically-assessed therapeutic agent containing Gd which has excellent tumor-cell uptake properties and has been used as a radiosensitizer for conventional whole-brain radiotherapy, particularly in the treatment of secondary brain metastases arising from non-small cell lung cancer. However, MGd was withdrawn from Phase III clinical trials in late 2007 due to an apparent absence of efficacy, and thus no suitable Gd agents are currently available for therapeutic use. Strategies employing Gd MRI contrast agents or Gd nanoparticles for NCT and PAT are being pursued but have either failed or only shown limited successes *in vivo* due to the low percentage of cell nuclei in brain tumors, for example, that incorporate Gd.

My group has developed the first examples of Gd^{III} complexes which include a triarylphosphonium functionality for tumor-cell targeting of mitochondria for NCT and PAT. We have also demonstrated their favorably low *in vitro* cytotoxicity in the absence of neutrons/X-ray photons, excellent *in vitro* tumor: healthy cell

selectivity, preferential localization within the mitochondria of treated cells, and a capacity to deliver remarkably high levels of Gd into human glioblastoma multiforme (T98G) tumor cells (up to 10¹¹ Gd atoms/cell, or ca. 3 000 ppm) by means of both ICP-MS analysis and synchrotron XRF quantitation. Such Gd levels far exceed those determined for MGd and Gd-containing DNA-binding agents, and lie well above the Gd thresholds calculated for efficacious GdNCT and GdPAT. The key results of this work will be presented.

PI Ch1 03

Development of novel boron carriers for BNCT

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Several monoclonal antibodies (mAbs), Ab fragments and glycans have been evaluated as putative human head-and-neck cancer (HNC) specific targeting units *in vitro*. Two Ab fragments showed efficient internalization by HNC cancer cell lines and were chosen for *in vivo* tumor localisation and biodistribution experiments in two HNC xenograft mice models. Both Ab fragments specifically accumulated into tumors at 24 h whereas control Ab fragments were not found in tumors. Average tumor vs. blood distribution ratio for one Ab fragment was 39 and 12 in two different xenograft mice models at 24 h. The blood clearance of Ab fragments in normal mice was much faster than for the whole mAb. Tumor accumulation and high tumor vs. blood distribution ratio are desired properties of a cancer targeting molecule for BNCT. Therefore, both Ab fragments have been developed further for boron conjugate synthesis. Boron clusters were attached to a biopolymer to form a polymeric boron compound, which was then conjugated to Ab fragments. Ab-boron conjugates with approximately 900 boron atoms were synthesized and tested for their functionality in the internalization assays with HNC cancer cells *in vitro*. Fluorescence microscopy revealed that boron conjugates were internalized efficiently by tumor cells. Control (normal) cells internalized the conjugates only minimally. Boron conjugates are currently being evaluated *in vivo* for tumor localisation and biodistribution in two HNC xenograft mice models.

PS1 C 1

An improved electronic collection of BNCT literature

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Two years ago a database for BNCT literature has been presented at ICNCT 15.

The purpose of this database was to make BNCT related publications available that cannot be found in main literature databases including proceedings, reports and monographs. In cooperation between Tsukuba University, University Duisburg-Essen and lately the Argentinian National Atomic Energy Commission CNEA, a literature database based on the software EndNote has been created collecting publications on BNCT. At the beginning, most of the articles only were available as hard copies. Recently major efforts were made to include in the database pdf files of the different documents. Up to now, approximately 25 % of the collected literature became directly available as electronic files. Recently, we started to scan older documents to extend the availability of the collection. Because of copyright aspects, a free distribution of this data compilation is not possible. However, an internal distribution to members of the International Society on Neutron Capture Therapy is feasible, if they are participating to further improve this data collection. ISNCT members interested to join our efforts and to work with the database are invited to contact the corresponding author.

PS1 C 02

A Strategy for the Success of BNCT in the Practical Situation

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The Great East Japan Earthquake Disaster and the Fukushima first nuclear power plant accident happened on 11th March, 2011. Thereafter I felt strongly that I should review the essence of the phenomena from the origin. And I realized immediately following two things: One is the social role and responsibility of a scientist or researcher. The other is to review the matters in my chosen field that is BNCT. From my personal experiences over 40 years, I have strongly believed that the BNCT field has been at a great turning point lately. The reasons are the following: (1) Switchover from nuclear reactor BNCT to accelerator based (acc-based) BNCT will decide the future of BNCT. I have felt that if acc-based BNCT system is not in use, there will be no further development of BNCT. (2) Applied technology has advanced rapidly in the all field of therapy. So, BNCT has to compete not only with the other modalities in the field of radiation therapy but also with other therapies such as surgical treatment, the chemotherapy and so on.

As to the future prospects, BNCT can contribute to the improvement of the field of radiotherapy by enabling a complementary relationship between different radiotherapy modalities. BNCT has the potential for providing patient-tailored cancer therapy by combining surgery, chemotherapy, etc, as necessary. At present, acc-based BNCT systems have advanced to the point where they can be widely put into practical use. Accordingly acc-based BNCT systems should be handled carefully in order to make the most useful contributions.

Like any other radiation treatment modality, BNCT has risks of induced cancers and normal tissue side effects caused by the neutrons and gamma rays. For the reduction of the risks, the doses of neutron and gamma ray should be low, for example, less than 200 mGy-Eq of whole body, and should be as low as possible for the healthy tissue in tumor part and its periphery. So, we need to clarify the weak points and risks of BNCT scientifically. And we need to find out the limits of the adaptation of BNCT.

In conclusion, we should have a strategy to assure the success of BNCT for practical situation. For instance, new design standard for acc-based BNCT should include the viewpoints of secondary cancer induced by BNCT. It is important that scientists and engineers should find not only a solution and/or reduction of faults and/or the risk, but also should inspect these characteristics scientifically with a positive point of view for the continued successful development of BNCT.

PS1 C 03

Overview of the re-initiation of BNCT clinical studies at the University of Tsukuba

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Background: Boron neutron capture therapy (BNCT) delivers tumor cell-selective, high linear energy transfer (LET) radiation without serious damage to surrounding normal tissue. BNCT might be effective and safe in patients with inoperable, locally advanced head and neck cancers (HNCs), even tumors that recur at previously irradiated sites. There are several advantages to applying BNCT to HNCs. First, the head and neck serve many important physiological and cosmetic functions. Surgery can have a substantial influence on the quality of life (QOL) of patients with advanced or recurrent HNCs. Therefore, organ preservation is of utmost importance. Second, many patients have squamous cell carcinoma (SCC) that recurs after intensive treatment, including surgery and chemoradiotherapy, and locally advanced non-SCC that cannot be controlled by conventional cancer therapy. Third, as HNCs exist superficially and are located not very far from the skin surface, it is possible to administer curative doses to the target with an epithermal neutron beam. Here, we provide an overview of the re-initiation of BNCT clinical studies at our institution.

Patients and methods

Indications for BNCT at our institution are as follows:

- (1) Newly diagnosed or recurrent locally advanced cancer.
- (2) Age 16 to 85 years.
- (3) Deepest part of the tumor within 7 cm of the skin surface.
- (4) A tumor/normal tissue (T/N) boron concentration ratio, obtained from (¹⁸F-boronophenylalanine [BPA]-PET), greater than 2.5.
- (5) Consent to perform BNCT from the patient and the patient's family.
- (6) ECOG Performance Status 2 or less.
- (7) Approval by our Medical Ethics Committee.

Patients were treated with BNCT at the Kyoto University Research Reactor (KUR). The T/N ratio obtained from ¹⁸F-BPA-PET was used for dose estimation before neutron irradiation and dose evaluation after BNCT. Neutron irradiation was performed with an epithermal beam at a reactor power of 5.0 MW (KUR) after intravenous administration of BPA in fructose solution at a dose of 500 mg/kg body weight. The tumor dose at the deepest part and the dose to both normal

skin and mucosa were planned to be more than 20 Gy-Eq and less than 15 Gy-Eq, respectively.

Discussion and conclusion: Previous reports have demonstrated that BNCT is a potential curative therapy for patients with head and neck cancer. The treatment does not appear to cause serious adverse effects, and may be used for either primary or recurrent disease. These excellent clinical results should have a major impact on future strategies for the treatment of head and neck cancer. We started conducting clinical studies of BNCT in 1994, but they were discontinued after an earthquake in 2011. However, we were able to resume clinical studies in March 2014. A longer duration of follow-up and a larger prospective study of accelerator-based neutron sources are needed to verify these initial results.

PS1 C 04

Clinical irradiation bed system with 3D-optimization algorithm for BNCT

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Abstract

The effect of boron neutron capture therapy (BNCT) is greatly dependent on the patient position in epithermal neutron irradiation. The two important issues should be resolved in a clinical irradiation bed. In the first, an exact posture setup is required there, resulting a patient is obliged to narrow posture maintenance during irradiation.

The second is the radio-activation in the patient irradiation bed. This issue can become a factor of an increase in the amount of whole-body exposures at a session of clinical irradiation. To reduce the radio-activation in the materials of the bed, we made the devices which reduce radio-activation of an irradiation bed, which was manufactured using the combined quality of the material which was suitable for the use. The clinical irradiation bed with 3D-control optimizing patient features was developed. Even if a patient's body movement was during irradiation, the optimization controls the patient posture for accelerator BNCT.

A control algorithm consists of the following element; (i) acquisition of patient 3D-image data from CT, (ii) virtual plane is assumed in 3D-CT image and an optimization of patient's posture without a stress, (iii) the posture of virtual space is automatically reproduced in irradiation room. In the system, CT image carries out a posture setup of the patient. After that, a patient will be transferred to an irradiation room and 3D-control system can set up a patient posture automatically based on virtual space setting CT conditions.

The reproducibility is less than 4 micrometers/10 mm in x, y, z-axes, and the accuracy of rotation and pitch is 0.1 or less degree. Matching verification between the bed movement and optimization algorithm is completed and the bed system is installed in the BNCT treatment room in the National Cancer Center in Tokyo.

PS1 C 05

Reduction of tumor uptake on interim ¹⁸F-FBPA-PET predicts the therapeutic response of boron neutron capture therapy

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Introduction

¹⁸F-FBPA-PET is used to evaluate the tumor uptake of boronophenylalanine (BPA) before boron neutron capture therapy (BNCT). In this study, we hypothesize that tumors had more reduction of ¹⁸F-FBPA uptake on interim ¹⁸F-FBPA-PET respond better to BNCT.

Materials and Methods

14 patients with recurrent head and neck cancers received two times of ¹⁸F-FBPA-PET evaluation and BNCT treatment were included in this study. Patients underwent pre-treatment and interim ¹⁸F-FBPA-PET imaging 1 week before 1st and 2nd BNCT treatment, respectively. Therapeutic response was evaluated by CT, MRI, or FDG-PET/CT. The SUVmax, SUVmean, metabolic tumor volume, and total FBPA uptake (SUVmean × metabolic tumor volume) of 1st and 2nd ¹⁸F-FBPA-PET were calculated and analyzed the correlation with tumor response.

Results

After two BNCT treatments, nine patients had significant response [three with complete response (CR) and six with partial response (PR)], while four patients had stable disease (SD) and one had progressive disease (PD). Δ SUVmax is significantly higher in the CR+PR group than in SD+PD group (46.3 % versus 20.6 %; $p=0.014$), while Δ total FBPA uptake shows a trend of correlation ($p=0.1$).

Conclusion

The reduction of tumor uptake on interim ¹⁸F-FBPA-PET could be a predictive value of BNCT treatment response. Further studies should be conducted to prove this concept.

PS1 C 06

Assessment of Carotid Invasion of Head and Neck Cancer to be Treated with Boron Neutron Capture Therapy

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Introduction

We carried out Boron Neutron Capture Therapy (BNCT) only to treated recurrent head and neck cancers (HNC) for which no effective treatment is left. Most of them are advanced case, and in some cases carotid invasions are experienced. In some cases of advanced carotid invasion BNCT might cause carotid rupture, that is Carotid Blowout Syndrome (CBS). CBS is one of the life threatening issues of HNC, so we should avoid this serious event.

Purpose

We should make guidelines for BNCT to avoid causing CBS, which never simply prohibit BNCT for advanced HNC but lead safe performance of BNCT.

Materials and Methods

I have reviewed literatures related CBS and radiation therapy, and have examined my own cases of carotid resection because of carotid invasion of HNC.

Results

The problems of carotid invasion cases planned to receive BNCT are below.

- (1) The carotid arteries are fragile and keep less self-regenerative power because of conventional radiation therapy in most cases.
- (2) The tumor reduction after BNCT might cause CBS in certain advanced case.
- (3) There are no guidelines to avoid CBS as far as I reviewed.

We have made a guideline to perform BNCT safely, which never prohibit BNCT for advanced HNC, but produce safe BNCT.

Conclusion

- (1) We need the guideline to perform BNCT safely.
- (2) We can not get much information to avoid CBS especially after conventional radiation therapy.
- (3) We head and neck group of BNCT have tried making a position paper for carotid invasion of HNC.
- (4) We should make a reliable guideline of BNCT for carotid invasion of HNC.

PS1 C 07

BNCT is an Effective Salvage Treatment for Recurrent Parotid Adenocarcinoma -A Case Report from Taiwan's BNCT Clinical Trial

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Abstracts: Introduction

Recurrent head and neck cancer is an intractable disease, including parotid adenocarcinoma. Surgery and radiotherapy are the mainstay treatment and usually this tumor is refractory to systemic chemotherapy. Salvage strategy for better disease control is difficult because of normal tissue tolerance.

Materials and Methods

In July 2013, the Taiwan's BNCT clinical trial recruited a 51 year-old patient with recurrent adenocarcinoma arose from left parotid gland. Before salvage BNCT, he underwent standard treatment protocol including surgery and adjuvant radiotherapy (66Gy/33 fractions) two years ago for the primary tumor. However, tumor recurred and extended largely to the left intracranial regions via skull base. Systemic chemotherapy (cisplatin and 5-FU) and target therapy (Avastin) were given but all were in vain. Tumor progressed rapidly in brain and intracranial pressure was increased (Karnofsky Performance Scale Index =50).

After craniotomy for partial reduction of tumor volume, two fractions of BNCT were exerted as salvage purpose separately within the interval of 30 days. Two T/N ratios of BPA were 4.56 and 3.73, respectively. BPA was dripped continuously during the therapy and total 460mg/BW (kg) was delivered. Two biological BNCT doses delivered respectively as 22.3 and 27.5 Gy-E at 80 % gross tumor volume. *THORplan* was used for dosimetry calculation.

Results

After BNCT, alopecia was the most adverse effects and the patient tolerated the whole treatment well. Dramatic tumor regression was observed by FDG-PET and MRI study in six months. More than 90 % of tumor volume was reduced which was similar to the results reported from Japan's study series (Kawasaki Medical School). Patient recovered well and return to work smoothly (KPS=80).

Conclusion

BNCT is an effective salvage treatment for recurrent parotid adenocarcinoma if the B-10 drug concentration ratio can be raised efficaciously.

PS1 C 08

BNCT and salvage therapy for a patient with multiform glioblastoma with over seven years survival and preserved performance status

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BNCT is an alternative cancer treatment to be advanced in the nearest future, which in theory might allow tumor-cell-selective high-dose radiation while sparing surrounding healthy normal tissues.

In our institutional experience on BNCT for 15 patients with newly-diagnosed multiform glioblastoma (GBM), the median overall survival (OS) and median time to progression (TTP) for all patients were 25.7 months (M) and 11.9 M, respectively. There was no significant difference in OS and TTP between intraoperative irradiation (OS: 23.3 M, TTP: 12.0 M) and external beam irradiation groups with additional X-ray irradiation (OS: 27.1 M, TTP: 11.9 M). However, the patients with long survival in our groups almost always need salvage therapy, which is different from the initial therapy.

We present a 32-year old woman who received BNCT in 2007 for the left frontal GBM followed by chemotherapy with temozolomide and the 2nd surgery. She continues to take antiepileptic drugs and she is living normal daily life without any speech disturbance, motor weakness, or cognitive function decline. Clinical course, pathological findings, and the impact of the initial and salvage treatments will be discussed.

PS1 C 09

Potential of Boron Neutron Capture Therapy for Malignant Peripheral Nerve Sheath Tumor

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Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a relatively rare soft tissue tumor with poor prognosis. Since almost 50 % of cases arise from type I neurofibromatosis (Von Recklinghausen disease), a genetic disorder dominantly autosomal, a number of MPNST patients is encountered each year. At present there is no effective treatment for MPNST other than surgical resection; therefore, establishment of a new treatment is needed. On the other hand, in recent clinical trials, the anti-tumor effect of BNCT has been demonstrated in 2 cases of mediastinal MPNST. We therefore analyzed the accumulation of boron in tumor cells after the administration of BPA to tumor-bearing nude mice transplanted with a human MPNST cell line. The results were compared with those of clinical BNCT cases to determine the effectiveness of BNCT on MPNST.

Materials and Methods

Cells from the human-derived MPNST cell line (HS-Sch-2) were cultured in media containing BPA at concentrations of 10, 20 and 30 µg 10B/mL (ppm), and the amount of 10B in the harvested tumor cells was measured by ICP-AES. The HS-Sch-2 cells were then subcutaneously transplanted into nude mice to generate a tumor-bearing animal model. After tumor formation, the animals were intravenously injected with BPA (24 mg 10B/kg b.w.), the dose for BNCT used in clinical cases. At predetermined intervals, both the tumors and the normal organs were excised and the time-dependent accumulation of 10B was measured by ICP-AES; also, the tumor-to-normal tissue (T/N) ratio was compared with that of the two clinical cases of BNCT.

Results

The cultured tumor cells showed a high uptake of ¹⁰B in a concentration-dependent manner. The concentration of ¹⁰B in the tumor cells of the tumor-bearing animal model reached 46.3 ppm at 30 minutes after the administration of BPA, which was higher than the minimum effective concentration of 20 ppm in BNCT 3 hours after the administration. Moreover, the T/N ratio was 2.5 and high enough to block radiobiological damage to normal tissue. On the other hand, although the T/N ratio of BPA by ¹⁸F-BPA-PET in the two clinical cases of MPNST was relatively low, 2.0 and 2.2, the tumor mass in both cases was suppressed by BNCT.

Conclusion

This study demonstrated not only a high accumulation of boron in MPNST cells *in vitro*, but also the selectivity of boron into the tumor cells of the tumor-bearing animal model, reinforcing the potential anti-tumor effectiveness of BNCT for clinical cases of MPNST.

PS1 C 10

Difference in 4-borono-2-18F-fluoro-phenylalanine kinetics between tumor and inflammation in rat model

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Introduction

4-borono-2-18F-fluoro-phenylalanine (FBPA) is a tumor-specific agent that is designed to depict the biodistribution of boronophenylalanine for boron neutron capture therapy (BNCT) of cancer. In this study, we aimed to explore the difference in the kinetics of FBPA between malignant glioma and inflammatory lesions.

Materials and Methods

F344 rats with C6 glioma cells 20 days after the transplantation and Wistar rats with inflammatory lesions 4 days after the subcutaneous injection of turpentine oil were scanned with micro PET/CT during 70 minutes post FBPA injection. Accumulation of FBPA was quantified in the tumor and inflammation on PET images by placing regions of interest with referring to CT images. Imaging data was analyzed by one-tissue-compartment model. The PET counts on the left ventricle cavity were used as the input function. Parameters including uptake rate constant K1 [ml/cm³/min], clearance rate constant k2 [1/min], and total distribution volume (Vt) were compared between malignant glioma and inflammatory lesions as well as SUVmax.

Results

Time activity curves of malignant glioma showed a characteristic pattern of rapidly increasing FBPA uptake up to 20 min and decreasing thereafter gradually, whereas FBPA uptake in inflammatory lesions was more stable and lower than in malignant glioma. Significant differences were observed for the pharmacokinetic parameters. K1, K2 and Vt were 0.48 ± 0.16 , 0.29 ± 0.06 , and 1.63 ± 0.23 in the malignant glioma, while 0.34 ± 0.05 ($p < 0.05$), 0.49 ± 0.08 ($p < 0.01$), and 0.70 ± 0.02 ($p < 0.01$) in inflammatory lesions, respectively. At 60 min after injection, FBPA SUVmax in malignant glioma and inflammatory lesions were 2.98 ± 0.14 and 1.59 ± 0.07 , respectively ($p < 0.01$).

Conclusion

We investigated the difference in FBPA kinetics between malignant glioma and inflammatory lesions in the rat model with micro PET/CT. These results may be of importance in the clinical application of BNCT because they suggest that boronophenylalanine might localize substantially more in tumor than in inflammation.

PS1 C 11

Evaluation for Radioactivation of Dental Materials and Draft for Measure Clinical Procedure on BNCT (Part 1) -Cobalt Chrome Alloy

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Evaluation for Radioactivation of Dental Materials

Popular dental prosthetic material, cobalt chrome alloy captures neutron on BNCT. Most significant nuclear is ^{60}Co . For 1 cm^3 volume with 1 hour BNCT radiation, 60Mbq/litre equivalent ^{60}Co will be synthesized. Its half time is 5.27 years and this alloy is kept in patients month for long time. So it should be avoided. And also within few years, for the re-treatment, dentist may try to remove this prosthetic, then radio active materials will be scattered.

Draft for Measure Clinical Procedure

Dental plate is to be removed before BNCT. If some problem for keeping environment mouth, mouth piece made by only acrylic resin should be used.

Crown bridge prosthetic should be removed. To avoid mastication disorder, temporal crown bridge made by acrylic resin or prosthetic made by only less radioactivating materials will be fine.

Also cobalt-chrome alloy has strong absorption for neutron. So neutron beam which should be radiated to the part will be decreased. In this point of view, cobalt-chrome alloy should be removed prior to BNCT.

To perform sure diagnostics for BNCT planning, dentist should attend to the medical team and should give opinion as well as proper dental treatment.

This procedure drastically reduces radiation exposure caused by induced.

PS1 Ch 01

Precious metal carborane polymer nanoparticles: potential for Boron Neutron Capture Therapy

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Organometallic precious metal complexes (Ru, Os) containing unusual boron-rich carborane ligands have potential as anticancer drugs, as Boron Neutron Capture Therapy agents,¹ and as bio-sensors.² The utilization of tools from nanotechnology, such as large drug delivery systems made of polymers, offers control of solubility and biodistribution of these organometallic complexes, and provides passive targeting *via* the EPR effect.³⁻⁵

We show that the size distribution, morphology, and stability of nanoparticles made of water-soluble poloxamer polymer⁶ and highly hydrophobic Ru^{II} and Os^{II} arene carborane complexes are highly dependent on the assembly conditions (*e.g.* temperature, complex loading). The formation and characterisation of core-shell micelles highly dispersed in water, and containing up to 600 boron atoms will be discussed. Preliminary data on *in vitro* anticancer activity, selectivity between healthy and cancer cells, cellular uptake, and neutron capture will be presented.

1. N. P. E. Barry and P. J. Sadler, *Chem. Soc. Rev.*, 2012, 41, 3264-3279.
2. N. P. E. Barry, R. J. Deeth, G. J. Clarkson, I. Prokes and P. J. Sadler, *Dalton Trans.*, 2013, 42, 2580-2587.
3. T. C. Johnstone, N. Kulak, E. M. Pridgen, O. C. Farokhzad, R. Langer and S. J. Lippard, *ACS Nano*, 2013, 7, 5675–5683.
4. N. P. E. Barry and P. J. Sadler, *ACS Nano*, 2013, 7, 5654-5659.
5. A. Pitto-Barry, I. Romero-Canelón, P. J. Sadler and N. P. E. Barry, *in preparation*.
6. A. Pitto-Barry and N. P. E. Barry, *Polym. Chem.*, 2014, DOI:10.1039/C1034PY00039K.

PS1 Ch 02

Synthesis of boron containing magnetic nanoparticles for potential neutron capture therapy

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The key for a highly efficient tumor therapy with minimal adverse side effects for the patient lies in the successful and specific delivery of the therapeutic agent to the tumor site. The combination of boron neutron capture therapy (BNCT) with Magnetic Drug Targeting (MDT) provides a very promising targeting approach. It involves the linkage of boron on superparamagnetic iron oxide nanoparticles (SPIONs), which – after intra-arterial application – can be focused to the region of interest by an external magnet. By this means the boron can be effectively enriched in the tumor region and the location of activity is confined by two mechanisms: Firstly, by the impinging neutron radiation and secondly, by the external magnet, which accumulates the boron-loaded SPIONs to a specific site of action.

In this study, we developed a boron containing SPION system in order to merge BNCT and MDT concepts. In the first step, steric stabilized dextran coated SPIONs were fabricated with a cold gelation process. Their agglomeration sizes decreased with increasing dextran content during coprecipitation and were in the range of 20 and 40 nm, as it was shown with dynamic light scattering measurements. Transmission electron microscopy images as well as X-ray diffraction analysis proved that the individual magnetite particles within those agglomerates were around 4.5 nm and monocrystalline. The small crystallite sizes led to the superparamagnetic behavior of the particles, which was exemplified in their magnetization curves, acquired with SQUID measurements. After amination of dextran coated SPIONs, the esterification with modified o-carboran was performed. The modification of o-carboran involved its treatment with *n*-BuLi and CO₂ in order to create a carboxylic acid group, which was confirmed with ¹H-NMR. The boron and iron concentration of the nanoparticles were determined with plasma coupled atomic emission spectroscopy (ICP-AES). Cell uptake and biological activity was investigated with the adherent VX-2 carcinoma cell line.

In conclusion, our results provide a promising delivery system in order DFG Excellencecluster to concentrate boron in the targeted area and open the opportunity for a successful combination of MDT and BNCT.

PS1 Ch 03

Gadolinium-loaded Chitosan Nanoparticles with Phospholipid-PEG Layer for Neutron Capture Therapy

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Introduction

Gadolinium neutron-capture therapy (GdNCT) can increase the possibility of hitting the target tumor cells with the long-range photons and/or a locally intensive destruction of DNA in tumor cells by Auger electrons. One of the key issues for success in GdNCT is to develop a device capable of delivering a sufficient Gd concentration into tumor. Our group has been developing intratumorally injectable gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs). The ultimate goal of the present study is to apply Gd-nanoCPs to a nano-device for delivering Gd to the tumor site via intravenous (i.v.) administration. For this purpose, a surface modification of the intact Gd-nanoCPs with soybean lecithin (SL) and PEG-lipid was carried out to provide stealth property to Gd-nanoCPs in systemic blood circulation. Then, their biodistribution was investigated in tumor-bearing mice *in vivo*.

Materials and methods

Gd-nanoCPs were prepared by using chitosan with a degree of deacetylation of more than 98 % and gadopentetic acid (Gd-DTPA) through our w/o emulsion-droplet coalescence technique. The Gd-nanoCPs thus prepared were dispersed in phosphate buffer solution (pH 7.0), surface-modified with SL and/or PEG-lipid (1,2-Distearoyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-2000], ammonium salt, AVANTI) by the thin-film hydration method, and then characterized in terms of their particle size, zeta potential and Gd-release in human plasma. Biodistribution of the surface-modified Gd-nanoCPs after i.v. administration was assessed using male B16F10 melanoma bearing C57BL mice at dose of 0.3 mg Gd/mouse. Gd analysis was carried out by an ICP-AES.

Results

The particle sizes of the intact Gd-nanoCPs, SL-coated Gd-nanoCPs and SL-PEG-lipid were 205, 208 and 143 nm, respectively. The particle size of the surface-modified Gd-nanoCPs was comparable or smaller compared to that of intact Gd-nanoCPs, possibly due to the improved dispersibility by surface-modification. The zeta potential of the intact Gd-nanoCPs was 27.6 mV, whereas that of SL-coated Gd-nanoCPs and SL-PEG-lipid coated Gd-nanoCPs became a negative value, i.e., -20.1 and -12.5 mV, respectively, indicating that the intact Gd-nanoCPs could be surface-modified with SL and PEG-lipid. The surface modification was also effective to suppress Gd-release from the Gd-nanoCPs in human plasma; Gd

release from the intact Gd-nanoCPs was completed within 3 h and that from SL-PEG-coated Gd-nanoCPs and SL-coated Gd-nanoCPs was suppressed to less than 60 % and 20 %, respectively, over 12 h. Biodistribution data revealed that after dosing of SL-coated Gd-nanoCPs, Gd concentrations in blood and tumor tissue were below the detection limit (< 0.2 ppm) and those in the reticuloendothelial system (RES) increased gradually and were higher than that of other organs. In contrast, Gd concentration in blood after dosing of SL-PEG-lipid coated Gd-nanoCPs was relatively high, i.e., $74 \mu\text{g Gd/g}$ wet tissues (ppm), and that in tumor tissue was 46 ppm even 12 h after dosing. While Gd concentration in blood was somewhat prolonged, a faster uptake of particles by spleen was seen, compared to SL-coated Gd-nanoCPs.

Conclusion

These results indicated that combination of SL and PEG lipid as surface-modifying agents would make it possible to stabilize Gd-nanoCPs in blood and thereby allowing a faster distribution of Gd to other organs including tumor mass. Further formulation consideration to achieve more enhanced stealth property of Gd-nanoCPs is under investigation.

PS1 Ch 04

Development of boron-containing polymeric drug delivery system for Boron Neutron Capture Therapy

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The Boron Neutron Capture Therapy (BNCT) isn't a new way to treat with the cancer, but still plays an important role in the clinical trial. There are two drugs for BNCT clinical trials: one is sodium mercaptoundecahydro-closo-dodecaborate (also called sodium borocaptate, $\text{Na}_2\text{B}_{10}\text{H}_{11}\text{SH}$, simplified as BSH), the other one is (L)-4-dihydroxy-borylphenylalanine (also called boronophenylalanine, simplified as BPA). These drugs are simple, low-toxicity, but still cannot satisfy the ideal requirement for BNCT usage. The ideal drugs for BNCT must have high boron concentration in tumor cells (about $20\mu\text{g}$ per tumor cell), high T/N (Tumor/Normal cell) ratio, and keep enough concentration in the tumor cells during the treatment process.

In the past twenty years, scientists have tried using the boron compound (such as boric acid, sodium closo-dodecaborate and carborane) to attach with amino acid, porphyrin, lipids and liposome, in order to enhance the selectivity. They have successfully improved the boron concentration in tumor cells. Recently, we have synthesized a new compound to achieve two goals: high selectivity and drug delivery to tumors. We chose a tetrabutylammonium closo-dodecaborate as boron-containing compound and attach to a polymer chain. We functionalized the boron cluster with a hydroxyl group in the end, and processed the ring opening polymerization to form the boron-containing polymer. This polymer comprised two blocks made by two monomers, lactide and 2-ethyl-2-oxazoline. The boron cluster attached polylactic acid (PLA) block is a hydrophobic part; the other block, poly-2-ethyl-2-oxazoline (PEOz) is hydrophilic part. While this boron-

containing polymer dissolves in the water, it will become a nano-scale micelle with the boron clusters assembled in the core of micelle, and it can significantly help the boron cluster to dissolve in the water. By the Enhanced Permeability and Retention (EPR) effect of nanoparticulate, we hope it could achieve a high level boron concentration in the tumor cells and also bring to a better T/N ratio.

PS1 Ch 05

Toxicity and boron uptake of carboranyl-containing porphyrin-cored dendrimers

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During the last years, we became interested in the development of different types of dendrons and dendrimers as platforms for the incorporation of boron-based clusters in order to obtain high boron-content molecules for further applications in biomedicine, most specifically in Boron Neutron Capture Therapy (BNCT).¹ The main goal of developing new compounds suitable for BNCT is to achieve an appropriate concentration and distribution of ¹⁰B in the tumor tissue. Boron clusters, such as dodecaborate, *ortho*-carborane, and cobaltabisdicarbollide have been one of the most important boron sources. Furthermore, boron clusters have shown high stability and can be easily functionalized to obtain a wide range of biocompatible derivatives.

It is well known that porphyrins can be selectively accumulated in tumor tissues and to continue there for long time. For that reason, one of the most promising BNCT agents during the last years has been the boron-containing porphyrins. A number of boron-containing porphyrins have been previously synthesized and evaluated in vitro and in vivo for use in BNCT.²

In this work, our aim is to obtain a high boron concentration in tumor cells, by using dendrimers as boron carriers. For that purpose, different generations of aryl-ether dendrimers with a porphyrin as core have been synthesized. Porphyrin dendrimers which contain 4, 8, 16 and 32 *ortho*-carborane cages linked to the periphery have been synthesized in very good yields by hydrosilylation reaction between appropriate carboranylsilanes and porphyrin dendrimers with terminal allyl groups. For all compounds, the reactions conditions have been optimized to afford a total functionalization of the starting porphyrin dendrimers, and finally compounds were purified. All compounds have been purified and characterized by usual techniques, such as FTIR, ¹H, ¹³C and ¹¹B NMR, UV-Vis spectroscopies, and elemental analyses. Some toxicity tests in two human cancer cell lines, Jurkat (T-cell leukemia) and Hela (cervical cancer cells) have been performed. Due to their limited water solubility, carboranyl porphyrin dendrimers were added to the cell cultures at 5.3 and 50 µgB/mL as DMSO solution (final concentration of DMSO lower than 1 % v/v), and were incubated for 48 h in the dark. The cell viability was evaluated by flow cytometry. The boron uptake was measured for some carboranyl porphyrin dendrimers following the previously described method.³

The preliminary biological results show that the majority of the tested compounds tested produce cytotoxicity because of the reduction in cell viability. However, the uptake results show no relevant boron concentration in the cells, so the diminution in cell viability could be due to nonspecific toxicity, but not because of their uptake. From these results, we find interesting to design new biological trials to get a cellular uptake, as encapsulation of carboranyl porphyrins so as to measure the boron concentration inside the cells following by cytotoxicity test.

¹ González-Campo A., Ferrer-Ugalde A., Viñas C., Teixidor F., Sillanpää R., Rodríguez-Romero J., Santillán R., Farfán N., Núñez R., *Chem. Eur. J.*, 19, 6299 (2013); Ferrer-Ugalde A., Juárez-Pérez E.J., Teixidor F., Viñas C., Núñez R.; *Chem. Eur. J.*, 19, 17021 (2013). ² Vicente M. G. H., Sibrian-Vazquez M.; Kadish K. M., Smith K. M. and Guilard R. (eds) *Handbook of porphyrin Science*; vol. 4, ch. 18, pp. 191-242 (2010); D. Pietrangeli, A. Rosa, S. Ristori, A. Salvati, S. Altieri, G. Ricciardi, *Coord. Chem. Rev.* 257, 2213 (2013) ³ Dahlström M., Capala J., Lindström P., Wasteson A., Lindström A., *J. Neurooncol.*, 68, 199 (2004); Capala J., Makar M.S., Coderre J.A., *Radiat. Res.*, 146, 554 (1996).

PS1 Ch 06

Feasible evaluation of WOW emulsion as intra-arterial boron delivery carrier for Neutron Capture Therapy to Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is one of the difficult to cure with operation, chemotherapy, or radiation therapies. Iodized poppy- seed oil (IPSO) have been used for hepatic arterial injection chemotherapy. We have been used water-in-oil-in-water emulsion (WOW) as the carrier of anti-cancer agents by modifying of IPSO on intra-arterial injections in clinical. It is necessary to accumulate ¹⁰B atoms in the tumour cells for effective boron neutron-capture therapy (BNCT).

In this study, we prepared ^{10}B SH entrapped WOW for application of BNCT to the treatment to HCC with selective intra-arterial infusion, and examine the size and ^{10}B concentration in tumour on time course after intra-arterial injection (IA) to verify the boron delivery property.

Materials and Methods

^{10}B SH-WOW had been prepared by double emulsifying technique, and was administered with IA via proper hepatic artery on VX-2 rabbit hepatic tumour models. The particle size distribution of WOW vesicles was determined using a laser-diffraction particle-size analyzer SALD-2000. The ^{10}B concentrations in VX-2 tumour on delivery with WOW was measured by ICP-Masspectroscopy at Jyuntendo University on 1, 3 days after IA.

Results and Discussions

The mean ^{10}B concentration prepared in ^{10}B SH-WOW was 10 000 ppm in this experiment. The size of WOW was controlled to 70 μm . The ^{10}B concentrations (ppm) in VX-2 tumour on delivery with WOW on 1, 3 days after IA were more than 170, 40, respectively. It was almost same decrescent time course in the ^{10}B concentration between two different surfactants composed of WOW. These results showed that WOW would be applied to intra-arterial boron delivery carrier of neutron capture agents on NCT to HCC.

PS1 Ch 07

Novel Phosphonium-Based Gadolinium NCT Agents

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Neutron capture therapy (NCT) is a treatment modality for glioblastoma multiforme which is the most common form of malignant brain tumor. The mitochondrial membrane potential of many types of cancer cells is known to be significantly higher than that of normal epithelial cells. This difference in potential allows for the selective accumulation of delocalised lipophilic cations (DLCs) such as tetraphenylphosphonium derivatives in cancer cell mitochondria. These DLCs can be linked to a thermal neutron-capturing nuclide such as the non-radioactive gadolinium-157 isotope, which possesses the highest neutron-capture cross-section of all stable nuclides (2.55×10^5 barns, 15.7 % natural abundance), to design new types of tumor-selective GdNCT agents. Such agents also offer great potential in related binary cancer therapies such as photon activation therapy (PAT). Eight new structurally-related arylphosphonium salts containing a xylyl linker and the macrocyclic ligand known as DO3A (1,4,7,10-tetraazacyclododecane-*N,N,N'*-triacetic acid) have been prepared in order to complex Gd(III) ions. These Gd(III) complexes were purified by reverse phase HPLC and characterised by high-resolution ESI-FT-ICR-MS. *In vitro* cytotoxicity assays of the Gd(III) complexes confirmed that they all possessed low toxicities in the absence of neutrons ($\text{IC}_{50} > 2 \text{ mM}$). Cell uptake studies were completed for selected Gd(III) complexes using the human glioblastoma (T98G) and human glial (SVG p12) cell lines, and their tumor selectivity ratio was determined. The key results of this work will be presented.

PS1 P 01

Evaluation of BNCT in-phantom parameters by response matrix methodY. Kasesaz¹, H. Khalafi¹, F. Rahmani²¹*Nuclear Science and Technology Research Institute (NSTRI), Iran*²*Department of Radiation Application, Shahid Beheshti University, Iran*

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The effectiveness of BNCT is dependent on the neutron beam parameters and Treatment Conditions (TC) such as tumour depth and size, as well as boron concentrations in normal and tumour tissues to evaluate the effectiveness of treatment, in-phantom parameters are defined: Therapeutic Gain (TG), Advantage Depth (AD), Therapeutic Depth (TD), Advantage Depth Dose Rate (AADR), Treatment Time (TT), skin dose rate and skull dose rate. TG must be as high as possible, and AADR, skin dose rate and skull dose rate must be as low as possible. AD and TD must be greater than tumours depth, and TT value must be reasonable (15 to 45 min). These parameters are dependent on the neutron energy and TC. Calculation of in-phantom parameters is time consuming procedure because of any changes in the therapeutic neutron beam and TC need another series of calculations. The Response Matrix (RM) method was introduced in ICNCT14 by F. Rahmani. This method is based on considering TC and calculating contribution of various dose components in phantom to calculate Response Matrix. Using RM method, mentioned in-phantom parameters could be calculated by a computer program in a very short time. In this paper behaviour of all in-phantom parameters relative to the neutron energy and TC condition have been investigated. The maximum allowable contaminations of the thermal and fast neutrons in a neutron beam have been calculated by RM method too. It was found that these values are 17.4 % and 2.6 %, for thermal and fast neutron, respectively.

PS1 P 02

Optimal neutron spectra calculation in BNCT by Geant4 codeZ. Badiyan¹, M. Firoozabadi², H. Zarif³, A. Sedghi⁴,¹*Zeinab sadat Badiyan, Department of Physics, Birjand University, Birjand, Iran*²*Mohamad Mehdi Firoozabadi, Department of Physics, Birjand University, Birjand, Iran*³*Hadi Zarif, Department of Physics, Ferdowsi University, Mashhad, Iran*⁴*Abolfazl Sedghi, Department of Power Engineering, Birjand University, Birjand, Iran*
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Calculating the optimum energy of incident neutrons is one of the important stages of treating cancer tumor by BNCT approach because the determination of the appropriate energy, increased the absorbed dose in tumor and reduced damage to normal tissue.

In this study we used Monte Carlo simulation with Geant4 code. At first, we designed head phantom with tumor, a spherical head phantom with radius of 11.3 cm along that carries 10ppm Boron and spherical tumor with radius of 2 cm that carries 43 ppm Boron and in distance of almost 2 cm from the scalp was considered.

For more real calculation, instead of using mono energetic neutron spectrum, we used Gaussian shape of neutron spectrum in the range 0.001 keV to 1 000 keV.

Afterward for different energies in this range, absorbed dose in the tumor and normal tissue obtained from boron, thermal neutron, fast neutron and gamma calculated and The total absorbed dose in the tumor and normal tissues were calculated with using these doses and specific RBE coefficients

Then we analyzed the obtained data with neural network in MATLAB and therapeutic gain was calculated.

Based on the result of simulation the most useful neutron energy range for tumor with the specifications above is 1-5keV was gained.

PS1 P 03

Study on the improvement of depth dose distribution using multiple-field irradiation in boron neutron capture therapy

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Introduction

It is important to improve the depth dose distribution for boron neutron capture therapy (BNCT) because neutrons do not reach to deeper part of human body. In order to improve the depth dose distribution, it is necessary to consider the use of the multiple-field irradiation and superior treatment beam. The superior treatment beams have been researched about optimized moderator for accelerator based neutron source. However, there is the physical limit to improve the depth dose distribution using the optimized treatment beam with single-field irradiation. In this research, the effect of multiple-field irradiation to improve the depth dose distribution was investigated by the simulation of the clinical studies at Kyoto University Research Reactor (KUR).

Materials and Methods

At Kyoto University Research Reactor Institute, over 470 clinical studies have been performed as of March, 2014. We evaluated the dose distribution with two-field irradiation with respect to several patients treated at KUR using calculation factors; those were used in clinical studies, such as the boron concentration and the boron concentration ratio of tumor to blood. The simulations were performed by SERA (Simulation Environment for Radiotherapy Applications). The simulation results of two-field irradiation were compared to the results of one-field irradiation. The quantitative comparison of the depth dose distribution was evaluated by the analysis of the dose volume histogram (DVH) for tumor.

Results

As a typical case, we show the simulation result of orthogonal two-field irradiation for head and neck tumor. The irradiation time was determined by the limit of the mucosa dose of 12 Gy-eq. In this case, the maximum tumor dose of two-field irradiation was same as that of one-field irradiation. However, the minimum tumor dose of two-field irradiation was 1.3 times higher than that of one-field irradiation. Furthermore, according to the results of DVH analysis,

it was found that the volume of tumor with the dose of more than 20Gy-eq was increased from 57 % to 72 %. Irradiation time of one-field irradiation was estimated to 41min. On the other hand, each irradiation time of two-field irradiation was 22 min and 33 min. At KUR, interval of time to change the setting position of patient between the irradiation is around 20 min. Total treatment time is estimated to 75 min.

Conclusion

The dose distribution of tumor was improved using multiple-field irradiation. However, treatment time was extended because of not only irradiation time but interval time to change setting position. From a view point of keeping boron concentration, treatment time should be short. If we can use more intense neutron source such as accelerator based neutron source with easy access to patient to change position, the treatment will be finished within one hour with keeping boron concentration. In the future, in order to improve the dose distribution, we will optimize the irradiation direction, the number of fraction and the weighting factor for each irradiation.

PS1 P 04

Bioneutronics: thermal scattering in organic tissues and its impact on BNCT dosimetry

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Neutron transport calculation is a key factor in BNCT numerical dosimetry assessments where thermal neutron flux is intimately related to the therapeutic boron dose. Although many developments on this topic have been performed during the existence of the therapy, there still are some concerns on the basics of neutron interaction phenomenon.

The default treatment for thermal neutron scattering in many transport codes is the “free gas treatment”, which neglects the chemical binding between the target nuclei. MCNP particle transport code, which is used as a gold standard in BNCT numerical dosimetry, includes many thermal libraries which account for the thermal motion of atoms and chemical binding states. However, the existing thermal libraries normally correspond to standard materials at some temperatures. Hydrogen, among all the elements involved in organic materials, is the most relevant for scattering interactions with thermal neutrons. Up to the moment, in an MCNP calculation for BNCT numerical dosimetry, only hydrogen bounded in bulk water was taken into account to describe thermal scattering in organic tissues. Nevertheless, tissues are composed by other substances that also contain hydrogen and even the water content cannot be considered in “bulk” state for a large fraction of its whole tissue distribution. This rise a very important question for BNCT dosimetry: how suitable is to take into account the phenomenon for hydrogen in bulk water neglecting the others? This work presents the beginnings of a study, with the intention of achieving a more realistic bioneutronics approach and of evaluating the impact on organic tissues and, specifically, BNCT dosimetry.

One of the first steps is studying the molecular dynamics of tissues in order to build a frequency spectrum which, afterwards, will be used to feed the NJOY nuclear data processing system to generate the scattering cross section libraries for each tissue. Preliminarily, numerical assessments of depth on-axis and radial flux profiles produced by external beams in cubic phantoms were performed to draw a bottom-line idea of the depth of the issue. A target of adipose tissue was chosen this time. This type of tissue is composed mostly of lipids (80 % mean value). In these macromolecules, hydrogen is mostly bounded to long chains of carbon atoms as is the case in polyethylene, which already has a thermal treatment cross section library. Then, two different thermal treatments for the neutron scattering cross sections were included in the simulations: i) hydrogen bounded in bulk water (typical treatment) and ii) hydrogen bounded in polyethylene (lipid-like compound). Calculations with MCNP were performed considering three different neutron sources: thermal source (Maxwell spectrum), epithermal source (1/E spectrum) and fast source (Watt spectrum).

The results show differences between the both thermal treatments. The relative difference in the on-axis flux calculation reaches values of: i) 10 % in the case of thermal source; ii) 10 % for thermal flux and 8 % for epithermal flux in the case of epithermal source; iii) 4.4% for thermal flux, 5.5 % for epithermal flux and 3 % for fast flux in the case of fast source. These are not large but statistically significant differences. With these values, thermal treatments choice would imply an important amount of systematic error in the dosimetry comparable of other typically found. This finding is encouraging to continue working on determining which tissues present these type of behavior and at what levels, and on building the basic bioneutronics knowledge to develop the tools to include the appropriate thermal scattering treatment.

PS1 P 05

A potential selective radiotherapy for ocular melanoma by sulfur neutron capture

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Introduction

Choroidal melanoma, the most frequent type of ocular melanoma, is a chemotherapy resistant cancer for which conventional radiation therapy is not a suitable treatment because the close proximity of radiosensitive structures (such as retina or optic nerve) requires the delivery of a high dose gradient between tumor and surrounding healthy tissues. As an alternative to surgical removal of the eye, the Collaborative Ocular Melanoma Study (COMS) recommend to use brachytherapy disk implants containing several seeds of I-125, a low energy gamma emitter. However, in many cases high dose gradient is not achieved and in delivering the minimal radiation dose required for tumor destruction (85 Gy) adverse effects may occur.

In order to achieve a dose gradient high enough to destroy tumor cells and spare healthy tissue in small structures inside the eye, a more selective radiation therapy is desirable. One of the authors showed that the selective presence of an isotope of sulfur, ³³S, in tumor cells would produce a sharp enhancement of the radiation dose delivered by a source of neutrons of an appropriate low energy (13.45 keV), by means of a resonance capture reaction. In this reaction, an alpha particle is emitted with a comparatively large energy (3.5 MeV) and radiation dose is deposited within the range of a cell size with a much higher biological effectiveness than photons. It is expectable that sulfur can be uptaken selectively by tumors via the enhanced metabolism of the malignant cells. A potential carrier for this purpose, 2-thiouracil, has been found to produce tumor-to-normal tissue uptake ratios greater than 50 in mice.

In this project, a novel idea based on sulfur neutron capture reaction applied for treatment of ocular melanoma is investigated by means of Monte Carlo simulations.

Methods

Monte Carlo simulations of a 13.5 keV circular neutron beam impinging on a human eye were performed to evaluate the outcome of a radiation therapy based on sulfur neutron capture. The model of the eye included the relevant anatomical structures, some of which are retina, cornea, optic nerve and tumor. The tumor is located in the choroid and contains a 10mg/g concentration of S-33 whereas the healthy tissue has a concentration of 1mg/g. The average total absorbed dose is calculated for each structure after neutron irradiation from different directions by using the MCNPX 2.5 code.

Results

Output from simulations show that for a given dose of 85 Gy in the tumor, the dose absorbed by healthy structures in the eye slightly varies depending on the direction of the neutron beam. In the best case, the dose absorbed by retina, macula and lens was 31.3 Gy, 27.0 Gy and 13.4 Gy respectively. The rest of the elements receive a dose below 20 Gy.

Conclusions

Monte Carlo simulations of sulfur neutron capture therapy for choroidal melanoma suggest that this treatment could potentially deliver high dose to tumor and spare radiation sensitive tissue including retina, lens and optic nerve. Feasibility of this procedure relies on the production of quasi energetic neutron beams which could be possible by collision of protons into lithium target via the ⁷Li(p,n)⁷Be reaction.

PS1 P 06

A Study of Effective Dose for Tumor in BNCT

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Introduction

In boron neutron capture therapy (BNCT) at Heavy Water Neutron Irradiation Facility of Kyoto University Reactor (KUR-HWNIF), boron dose is estimated based on the following equation: boron dose = $C_{BPA} \times R_{T/B} \times CBE_{BPA} \times D_{BPA} + C_{BSH}$

$\times CBE_{BSH} \times D_{BSH}$. Here C: boron concentration (ppm), $R_{T/B}$: ratio of tumor to blood (T/B ratio) for BPA, CBE: compound biological effectiveness, D: physical dose per 1ppm of boron-10 (Gy/ppm). The used boron concentration is for whole blood. The degree of BPA uptake for tumorous cell is expressed using T/B ratio based on whole blood. In clinical study, T/B ratio is decided using the result by F-BPA-PET. However, BPA uptake is smaller than T/B ratio, or almost zero in some actual tumorous cells. Therefore, we are reconsidering the definition of tumor dose. In this presentation, one of the studies for effective dose for tumors in BNCT is reported.

Materials and Methods

Tumor dose was re-estimated for the recent BNCT clinical studies, performed at KUR-WNIF. The boron dose for tumor due to BPA was assumed to be as follows. The conventional dose based on T/B ratio was considered to be the sub-maximum-estimated dose, and CBE was assumed to be 3.8. For the minimum-estimated value, boron dose was considered to be similar to that for BSH, as BPA exists just surround the cell. CBE was assumed to be 2.5, the same for BSH. At present, dose estimation is performed using boron concentration of whole blood, both for BPA and BSH. The used CBEs and T/B ratio are decided also based on boron concentration of whole blood. In actual, the surrounding of cell is filled with not blood but interstitial fluid. It can be assumed that the concentration in interstitial fluid equals the concentration in plasma. Accordingly, boron dose for tumor was assumed to be as follows. The boron concentration for whole blood was used in maximum estimation. In minimum estimation, the boron concentration for plasma was used.

Results and Discussions

In BNCT performed at KUR-HWNIF from 2012 to 2013, 39 irradiations were for head and neck tumors with BPA only, 41 irradiations for brain tumors with BPA only, and 14 irradiations for brain tumors with BPA and BSH. From the measured data of these irradiations, the ratio of plasma to blood (P/B ratio) for BPA is 1.28 ± 0.08 in average. In the while, the average P/B ratio for BSH is 1.44 ± 0.09 , and it is larger than that for BPA. The minimum-estimated dose and sub-maximum-estimated dose were re-estimated for the three respective BNCT irradiations in three groups such as head and neck tumors, brain tumors with BPA only, and brain tumors with BPA and BSH. For the irradiations with BPA only, the ratio of minimum-estimated dose to sub-maximum-estimated dose (Min./Sub-Max. ratio) was 20~40 %. As T/B ratio increased, Min./Sub-Max. ratio tended to decrease. For the irradiations with BPA and BSH, Min./Sub-Max. ratio was 40~55 %. It was larger at 15~20 %, compared with the irradiations with BPA only.

Conclusion

Based on the results of the re-estimation for tumor dose, the target dose should be decided in consideration of the minimum-estimated dose, for the larger T/B ratio. In actual, the cells with larger BPA-uptake and smaller BPA-uptake are mixed. There is thought to be an "effective dose", between Min. and Sub-Max.-estimated doses. Comparison of the clinical effects for the BNCTs with the similar sub-maximum doses is needed. For the smaller-effect case, it is suspected that many cells didn't uptake BPA. So, the effective dose is close to Min.-estimated dose. For the larger-effect case, the effective dose is close to Sub-Max.-estimated dose.

PS1 P 07

About radiations from gadolinium at Neutron Capture Therapy

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The keystone to success of radiating therapy is creating an exact necessary dose in the affected place of human body. For creation of a necessary dose in GdNCT are required local sufficient concentration gadolinium in a tumour and an exact estimation of nuclear radiations appearing in natural gadolinium at irradiating with epithermal neutrons beam. For definition of gadolinium concentration in bodies, it is necessary pharmacokinetics studying of used preparation. For an estimation of the absorbed dose from gadolinium nuclear radiations, it is necessary exact measurements of these radiations.

Natural gadolinium consists of seven isotopes: ^{152}Gd (0,205 %), ^{154}Gd (2,23 %) ^{155}Gd (15,10 %), ^{156}Gd (20,60 %), ^{157}Gd (15,70 %), ^{158}Gd (24,50 %), ^{160}Gd (21,60 %). From them ^{155}Gd and ^{157}Gd have very great cross sections (n, γ)-reactions. There are different estimations of the contribution to a total dose of the secondary particles arising at the nuclear reaction with neutrons in these isotopes natural gadolinium. From that main are reactions of capture of neutrons ^{155}Gd (n, γ) ^{156}Gd and ^{157}Gd (n, γ) ^{158}Gd which together give >90 % of the contribution on the absorbed dose [1].

However, the analysis of full neutron cross sections for isotopes natural gadolinium [2] shows, that dependence of section on energy of neutrons has resonant peaks in the energy region $10^{-6} - 0.01$ МэВ, i.e. in energy region of epithermal neutrons. These resonances can make the essential contribution to absorbed dose at irradiation deep located tumours. Therefore at GdNCT with application epithermal neutrons beam it is necessary to estimate contributions and others radiations.

From them the most considerable is (n, γ) reactions in ^{152}Gd и ^{155}Gd , (n, t) in ^{154}Gd , (n, 2n) for ^{156}Gd , ^{157}Gd и ^{158}Gd . Also (n, γ) in ^{158}Gd where the excited nuclei ^{159}Gd becomes β -active and also (n, γ), (n, 2n), (n, p), (n, d) reactions in ^{160}Gd . Decay processes of excited nuclei with emission of γ -radiations, internal conversion electrons, Auger electrons and characteristic x-ray radiation requires of estimation. In this article the contribution these reactions in natural gadolinium to the summary dose for GdNCT is defined.

1. G. A. Kulabdullaev et al. *Uzbek physical journal*, 2013, V.15, № 4, 127-138.

2. G.A. Abdullaeva et al. *Atomic energy, Russia*, 2013, V115, 3,166-170.

PS1 P 08

Dedicated target based on micro-channel geometry for the generation of neutron beams for BNCT

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One of the actual tendencies in Boron Neutron Capture Therapy (BNCT) is the transition from nuclear reactors to accelerator based neutron sources. Accelerator based neutron sources cannot produce thermal neutron beams with fluxes comparable to nuclear reactors. In addition to this, the use of BNCT for the treatment of deep-seated tumours requires neutron beams of higher energy, hence epithermal energies (1-50 keV), and important intensities. Epithermal neutron beams can be produced by means of different reactions and many researchers have studied different options. For instance, $^{13}\text{C}(d,n)^{14}\text{N}$ reaction at $E_d = 1.5$ MeV would require 100 mA for 15 min treatment [1]. In the same work [1], $^7\text{Li}(p,n)^7\text{Be}$ is proposed as the most suitable reaction at $E_p = 1.95$ MeV requiring 5 mA. The current status on the development of low energy and high intensity accelerator suggests that $^7\text{Li}(p,n)^7\text{Be}$ may be the most suitable one from the point of view of accelerator development. In order to maximize the neutron flux a very narrow primary proton beam has to be used, so the target has to remove a very high density power, as well as metallic Lithium is preferred because of the higher neutron yield than other Lithium compounds. The major drawback of this reaction is that metallic Lithium has a low melting point (181° C) and low thermal conductivity (84 W/(K·m)). Moreover Lithium is a very reactive material, forming lithium oxide immediately upon exposure to air. Also tensile strength is very low. Hence, Lithium targets are formed by attaching Lithium layer to a backing material. The evaporation technique is the preferred one since the thickness can be the minimum to decrease the proton energy below the threshold. In this case the proton beam is stopped in the backing and the power sustained by the Lithium the lowest possible. Currently available Lithium targets are inadequate to sustain the high density power that needs to be dissipated in BNCT applications. We have designed and constructed a low mass copper backing from a solid piece of Copper UNSC15720 by EDM drilling of consecutive holes of 0.5 mm diameter and 15 mm length [2]. We present the results of some tests with water as coolant. A first test was performed with a Tungsten Inert Gas welding machine to mimic the beam spot. The test showed that 3.4 kW/cm² can be sustained keeping the surface temperature below 150° C. A second test was carried out at PATON Institute (Kiev, Ukraine). The target core has been placed in a vacuum chamber at 10⁻⁴ mm and heated with 1 cm diameter electron beam of 60 kV and a maximum current of 74 mA. Hence, more than 4.4 kW/cm² were sustained by the backing with the temperature of the surface to the beam below 150° C. Concerning the coolant, liquid metals seem to have the best performance. The thermal conductivity combined with the specific heat capacity can be compressed in the Prandtl number which, together with the Nusselt number, enter in the definition of the film h coefficient. In order to increase the heat removal efficiency, the film h coefficient has to be maximized. The GalnSn seems to be the best option and it is commercially available. We present finite element method calculations of the surface temperature to compare water and GalnSn alloy as coolants.

[1] E. Biseeglie et al., Nucl. Inst. And Meth. A 476 (2002) 123-126.

[2] P. Mastinu, J. Praena et al., Phys. Procedia 26 (2012) 261-273.

PS1 P 09

Application of a statistical model for the evaluation of the gamma dose in BNCT Monte Carlo simulations.M. P. Sabariego¹, I. Porras¹ and P. L. Esquinas²¹Departamento de Física Atómica, Molecular y Nuclear, Universidad de Granada, Granada, Spain, ²Department of Physics and Astronomy, University of British Columbia, Vancouver, Canada. email: msabarie@terra.com

In Boron Neutron Capture Therapy (BNCT) of cancer, Monte Carlo (MC) simulation of neutron transport becomes an essential tool for calculations of the dose delivered because of the complex interactions of neutrons in tissue. The radiation delivered in BNCT consists of a mixed field of secondary particles with high and low linear energy transfer (LET) values -therefore a different relative biological effectiveness (RBE)-. The absorbed dose is usually separated in four main components: thermal neutron, fast neutron, photon -primarily 2.224 MeV gammas from $^1\text{H}(n,\gamma)^2\text{H}$ radiative capture reaction-, and ^{10}B dose -from the reaction $^{10}\text{B}(n,\alpha)^7\text{Li}$ -. Two reasons make the photon dose evaluation to become essential, specially for healthy tissue. First, due to the nature of photon interaction with matter -mean free path for 2 MeV gamma is 20.4 cm in soft tissue [1]-, it is likely that part of the photon dose will be delivered outside the target volume, affecting normal tissue. Second, the photons are produced by the capture of thermal neutrons which are spread in the medium. In particular, the latter reason causes a loss of statistic for the MC evaluation of dose delivered. Therefore, it is required to simulate a higher number of primary neutrons in order to achieve enough accuracy in photon dose estimation, which implies an increasing computation time. Reference MC calculations of BNCT based on the use of kerma/fluence factors approximate this dose component by the photon kerma [2], using tabulated factors, with a loss of accuracy with respect to the other dose components.

The aim of this work is the fast and accurate evaluation of the photon dose by the use of a statistical method developed for point-like sources [3]. First, the number of photons generated via radiative capture in a particular cell is obtained using the Monte Carlo code MCNP5 [4]. Then, this photon map is used as a multiple point source input for the statistical model and its dose is calculated in a rapid and precise way. Finally, the results will be compared with full simulations of photon dose in BNCT and the simplicity of its application to an in-house neutron transport code will be discussed.

[1] J H Hubbell and S M Seltzer. *Tables of X-Ray Mass Attenuation Coefficients and Mass Energy-Absorption Coefficients from 1 keV to 20 MeV for Elements Z = 1 to 92 and 48 Additional Substances of Dosimetric Interest*. Radiation and Biomolecular Physics Division, PML, National Institute of Standard and Technology.

[2] J T Goorley, W S Kiger III and R G Zamenhof, "Reference Dosimetry Calculations for Neutron Capture Therapy with Comparison of Analytical and Voxel Models". *Med. Phys.* 29 (2), 145-156 (2002).

[3] M P Sabariego, I Porras and A M Lallena, "Simple analytical expressions for the dose of point photon sources in homogeneous media", *Phys. Med. Biol.* 53, 6113-6128 (2008).

[4] X-5 Monte Carlo Team, 2003; LA-UR-03-1987, (2003).

PS1 P 10

Boron Neutron Capture Therapy for Breast Cancer in Pregnancy: A Simulative Dosimetry Estimation StudyY. Rezaei Moghaddam¹, E. Hoseinian Azghadi¹, L. Rafat Motavalli¹, H. Miri Hakimabad¹, Y. Li²¹Physics Department, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran²China Institute of Atomic Energy, Beijing 102413, China
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Cancer complicates approximately 1 per 1000 pregnancies and causes one-third of maternal deaths. Pregnancy affects the treatment procedure and causes lots of limits in prescribing radiotherapies considering the fetus receiving dose. Especially in the case of breast cancer which is a common cancer in women, radiotherapy is hardly prescribed in the first and second trimester of pregnancy. Instead, surgery is usually suggested especially for the locally advanced tumors. In these situations, neutron capture therapy can be mentioned as a possible treatment: considered as a targeted therapy, avoid the high fetal dose and also conserve the breast. In this study, dose assessment is performed by MCNPX 2.6.0 using new developed pregnant phantoms in Ferdowsi University of Mashhad based on magnetic resonance (MR) images tied to the International Commission on Radiological Protection (ICRP) reference voxel phantom. The phantom is developed for two cases of 3 and 6 month pregnant. The neutron beam source is extracted from the both thermal and epithermal output of In-Hospital Neutron Irradiator (IHNI) of Beijing, China. The neutron beam with the 6 cm radius is employed to the treated volume (breast) in five different orientations. No shielding is considered in the abdominal area.

Six different locations, each with four different tumor sizes, in the breasts of both 3 and 6 month pregnant phantoms (totally 24 situations) are considered as tumor volumes. In each breast, one case is assumed to be deep-seated and two others are near-surface. Each tumor volume is irradiated in five orientations: straight to the breast (anterior-posterior) and the other four items with 45 degree rotation in right, left, up and down of the right breast. RBE-weighted absorbed dose values are estimated for thermal and epithermal beams of IHNI. The optimum multi-beam irradiation for each tumor volume is obtained based on: total dose to fetus and its sensitive organs, tumor to normal tissue dose ratio, and dose uniformity in tumor volume. Based on these calculations, we conclude that BNCT can be applied to breast cancer in the pregnant women.

PS1 P 11

Experimental trial of measuring spatial distribution of neutrons and gamma rays in BNCT using multi imaging plate system.Kenichi Tanaka¹, Yoshinori Sakurai², Satoru Endo³, Hiroki Tanaka², Jun Takada¹¹Center of Medical Education, Sapporo Medical University, S1W17, Chuo, Sapporo 060-8556, Japan.²Research Reactor Institute, Kyoto University, 2-1010, Asashiro-nishi, Kumatori, Sennan, Osaka 590-0494, Japan³Quantum Energy Applications, Graduate School of Engineering, Hiroshima University, 1-4-1 Kagamiyama, Higashi-Hiroshima 739-8527, Japan.

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Abstract

In accomplishing the quality assurance and quality control for neutron capture therapy, handy detection system for the distributions of neutrons and gamma rays is one of the potential and essential options. This study tries to use the imaging plate for this purpose. Previously, the configuration of the converter to enhance and separate the neutron and gamma ray components was investigated using Monte Carlo calculations with the code PHITS. This paper describes the experimental verification of this method.

The converter configuration utilized was determined referring to the previous proposal by the simulation using PHITS calculation. From upstream of the neutron and gamma ray beam, the converter consisted of 6 mm thick carbon for gamma rays, 2 mm thick epoxy with 6.85 wt % ¹⁰B for thermal neutrons, and 4 mm thick epoxy with 6.85 wt % for epithermal neutrons. Each layer had the imaging plate in its center, e.g. at 3 mm depth for carbon, etc. Detecting fast neutrons was not tried in this study because the sensitivity to the fast neutrons was very low, e.g. a few % of the total for the configurations previously investigated. The imaging plate used was "BAS-TR" by Fuji Film Corporation, Japan. The irradiation was performed with the standard epithermal neutron irradiation mode at heavy water neutron irradiation facility at Kyoto University Research Reactor Institute. The fluence of each beam component was determined by solving the equations about the imaging plate signal and their sensitivities for components. Here, the sensitivities were determined with the PHITS calculation in advance.

As a result, plausible fluence distributions of epithermal neutrons and gamma rays were obtained. However, obtained results for thermal neutrons were negative values and were not appropriate. This may be due to low contribution of thermal neutron component to the energy deposition of the imaging plate in PHITS calculation, at most 8 %. However, this study demonstrates the validity of the multi imaging plate system in measuring the fluence distributions of certain components, and suggests that optimizing the enhancer configuration according to the neutron/photon field will improve the performance. Further attempts to improve the equations and resultant distributions will also be presented.

PS1 P 13

On the Importance of a Dedicated Beam Monitoring System for BNCT FacilitiesDer-Sheng Chao¹, Yuan-Hao Liu¹, Shiang-Huei Jiang²

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The beam monitoring system is indispensable to BNCT facilities to achieve an accurate patient dose delivery. The beam monitoring of a reactor-based BNCT (RB-BNCT) facility can be implemented through the instrumentation and control system of the reactor provided that the spatial distribution of neutron flux in the reactor core remains constant during the reactor operation. However, due to the fuel depletion, poison production, control blade movement etc., which depend in a complicated manner on the neutron flux, some extent of variation may occur in the spatial distribution of the neutron flux in the reactor core. Consequently, there may be a variation in the neutron beam extracted from certain part of

the reactor core even when the reactor operates at a constant power, which is normally determined and maintained by specific fission chambers at different corners of the reactor core. Therefore, a dedicated beam monitoring system is required to be installed in the RB-BNCT facilities.

In this work we investigated the readings of the three beam monitors of the BNCT facility at Tsing Hua Open-pool Reactor (THOR) and compared them with the readings of the two fission chambers of the THOR control system. The correlations of the readings of three beam monitors with each other and with the readings of the two fission chambers were evaluated. It was found that in around 30 periods of measurement within 16 days the fluctuations of ratios between readings of beam monitors lay within 0.2%, however, the ratios of readings between the two reactor-control fission chambers and one of the beam monitors showed fluctuations of 5.9 % and 17.5 %, respectively.

PS1 P 14

Development of the real-time neutron monitor with a LiCAF scintillator

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The measurement of thermal neutron flux is necessary for boron neutron capture therapy (BNCT) to realize safety treatment, especially during the irradiation by an accelerator neutron source. Currently, the flux is estimated by the radio-activation of the gold foil or wire, because the gamma-ray intensity from the gold is correlated to the amount of the irradiated thermal neutrons. The gold activated method is in batch mode and needs a long time to get the neutron flux, while the scintillator with a fiber works as a real-time monitor. It is also used for detection of an enormous condition of the accelerator. The plastic scintillator with a plastic fiber was already applied to BNCT irradiation field; however the deterioration caused by the radiation damage was reported. We developed the real-time neutron monitor, which is hardly affected by the radiation damage.

The detector part consist a small grain scintillator, an optical quartz fiber and a photo-multiplier tube (PMT). The scintillator called LiCAF is used in the detector. LiCAF that is the crystal of LiAlCaF_6 (Eu doped) produced by Tokuyama Corporation in Japan has a good discrimination ability of neutrons from gamma-rays as the background. The discrimination of neutron-gamma was confirmed by the irradiation test at the heavy water facility at Kyoto University Reactor (KUR). In this presentation, the radiation hardness of the detector components, the stability improvement and the influence in the neutron field are reported.

At first, the radiation hardness of the scintillator and the optical fiber was tested individually by measuring of the degradation of the light yield and the transparency. The maximum amount of irradiated neutrons is 4×10^{14} n/cm² and 1×10^{14} n/cm² for the scintillator and the fiber, respectively. As a result, there was no degradation during irradiation for the scintillator and the fiber. These results show that the detector could be handled without any degradation of the scintillator and the fiber in more than 110 hours and 28 hours at 1×10^9 n/cm²/s, respectively.

At second, the stability of the detector response was also measured at KUR. The

neutron detection efficiency was fluctuated about 15 % in an hour because of PMT gain drift. To correct the drift effect, the software that have online analysis algorithm was developed. By using the software, the fluctuation decreased to ~ 5 %.

Finally, the influence of the detector in the neutron fields was estimated by using a simulation code PHITS 2.52. The result shows that the flux behind the detector is decreased 4.5 % by the scattering effects.

PS1 P 15

Measurement of Neutron Parameters in the Neutron Beam exit of IHNI

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The In-Hospital Neutron Irradiator (IHNI) is specially used for Boron Neutron Capture Therapy (BNCT). On the both sides of the reactor core, there are two neutron beams, one is thermal neutron beam, and the other opposite to the thermal beam, is epithermal neutron beam. A small thermal neutron beam is specially designed for the measurement of blood boron concentration by the prompt gamma neutron activation analysis.

The neutron flux at the exit of neutron beams are measured by gold foil activation method and solid state nuclear track detector (SSNTD) method separately. Neutron flux distribution and neutron spectrum are measured by multiply foils activation method and unfolded by SAND-II program.

The neutron flux of the thermal neutron beam is $1.61 \times 10^9 \text{ n/cm}^2\cdot\text{s}$ by Gold foil activation method, and $1.50 \times 10^9 \text{ n/cm}^2\cdot\text{s}$ by solid state nuclear track detector method; Neutron fluxes of epithermal neutron beam and experiment neutron beam are $2.20 \times 10^7 \text{ n/cm}^2\cdot\text{s}$ and $2.91 \times 10^6 \text{ n/cm}^2\cdot\text{s}$ respectively by solid state nuclear track detector method.

The discrepancy distribution of thermal beam is less than 8% in the area of $R < 3$ cm in the center of the exit, while the discrepancy distribution of Epithermal beam is less than 10% in the area of $R < 3$ cm; the percent of thermal neutrons is over 90 % in the thermal neutron beam. Neutron flux, distribution and spectrum results show that the neutron beams of the IHNI meet the designed requirements, and can be used for BNCT.

PS1 P 16

Photon-neutron mixed field dosimetry by TLD700 glow curve analysis and its implementation in whole body dose monitoring for BNCT treatments

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Introduction

The thermal neutron fields suitable for boron neutron capture therapy (BNCT) are characterized by very high neutron flux and low gamma dose. Determination of each dose component involved is not an easy task. This work shows a method of computing the photon dose and the thermal neutron fluence from the glow curve (GC) of a single ${}^7\text{LiF}$ thermoluminescence detector. Knowing the dosimeter calibration of each radiation is the unique condition. Photon dose evaluation from the GC of a TLD-700 does not require calculation or measurement of the thermal neutron fluence in the positions of dosimeters, but only the knowledge of the shape of the GC of a TLD-600 exposed to a neutron field. This method was proposed and first used in the TAPIRO research reactor (Casaccia, Italy) and in the TRIGA MarkII of LENA reactor (Pavia, Italy) by the group headed by Dr. Grazia Gambarini. Evaluations made in order to be properly applied in the BNCT RA-6 Research Reactor facility are shown. In addition, MatLab software was developed as an analysis tool. Finally, the method is implemented in dose monitoring of a patient undergoing a BNCT treatment using a whole body phantom to compute the photon and thermal neutron absorbed according to this methodology.

Material and Methods

The dosimeters used were TLD-600 (${}^6\text{LiF:Mg,Ti}$ 95.6 % ${}^6\text{LiF}$) and TLD-700 (${}^7\text{LiF:Mg,Ti}$ 99.9 % ${}^7\text{LiF}$) from Harshaw. The method requires the knowledge of photon and thermal neutron calibration GCs of the TLD-700 and a GC of a TLD-600 irradiated with thermal neutrons. To evaluate the contribution of photons to the TL emission of a TLD-700, the dosimeter was calibrated in a known field of Cs-137. When this calibrated curve is subtracted, point by point, from the TLD-700 GC irradiated in a mixed field, the result is the contribution of thermal neutrons to the TL emission and it has a very similar shape to that of the TLD-600 after exposure to a thermal neutron field (with a different scale). This feature is used to obtain both the gamma dose and the thermal neutron fluence from the GC of a single TLD-700. The GC analysis of the dosimeters was done by the initial rise method and built-in Matlab functions. The whole body dosimetry in BNCT treatments was performed by using a BoMAB phantom (Bottle Manikin Absorption), with measurement points as representative of critical organs.

Results

Implementation results and methodology evaluation are satisfactory and comparable with measurements carried out during the beam dosimetry characterization, performed with paired ionization chamber method and activation detectors. The whole body phantom implementation highlights the precision, simplicity and strength of the method in comparison with the usual methodology.

Conclusions

The GC method shows the potential to estimate both gamma dose and thermal neutron fluence by using a single TLD-700, resulting in a simple, fast a low uncertainty method.

PS1 P 17

Neutron flux assessment of a neutron irradiation facility based on inertial electrostatic confinement fusion

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Neutron production from fusion reactions has been an important concern since the beginnings of fusion science and technology. Fusion field of study, mostly devoted to energy production, has been focused in neutrons as undesired by-products of fusion combustion of deuterium and deuterium-tritium fuels. However, there have also been researches and developments that thought of fusion as a safe manner for production of neutrons for different applications and gave birth to a broad family of compact fusion-based neutron generators. These are small fusion reactors based on confinement principles different from those of reactors designed for energy production and can be built on a lab-bench scale. The combination of size, relative ease of construction and operation, and safety levels have made of them a tempting possibility for their utilization in medical environments where neutrons are required and, specially, for Boron Neutron Capture Therapy (BNCT).

The main limitation for their application to BNCT has been the small levels of obtainable fluxes. Nevertheless, recent developments have brought successively increasing performances and promise to continue the production rate growth. One of the most promising devices are those based on inertial electrostatic confinement (IEC) fusion, which have been showed to be simple, reliable, durable, and one of the most compact ones. Accordingly, this work considers this type of generators as a potential neutron source for a neutron irradiation facility that could be installed in a health care center as well as in research areas. This study is an extended flux distribution analysis that aims at introducing a facility that can match BNCT neutron flux requirements.

The chosen facility configuration is “irradiation chamber”, a dozen-centimeter-sized cavity near or in the center of the facility geometry where samples to be irradiated can be placed. The rest of the facility contains neutron generators and structures to give neutrons the appropriate spectral distribution and provide an appropriate shielding. Neutron flux calculations were basically designed to study different manners for improving scattering processes and, consequently, optimize neutron flux in the irradiation position. The study extends from considering utilization of materials such as graphite, heavy water, and bismuth, to evaluate geometric setups with variations of structure sizes and source-to-irradiation position distances. DT and DD fusion reactions were considered. Flux distributions were assessed through numerical simulations of several models implemented in MCNP5 particle transport code.

Simulation results provided a wide spectrum of combinations of net fluxes and energy spectrum distributions. Between the different models, one can find a group that can provide thermal neutron fluences per emitted neutron in a range from $4.1 \times 10^{-4} \text{ cm}^{-2}$ to $1.6 \times 10^{-3} \text{ cm}^{-2}$ with epithermal-to-thermal ratio between 0.3 % and 13 % and fast-to-thermal ratio between 0.01 % to 8 %. Under these conditions, neutron production rates larger than $6 \times 10^{11} \text{ n}\cdot\text{s}^{-1}$ would be required to obtain thermal neutron fluxes above $10^9 \text{ n}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$, typical for BNCT clinical practice.

IEC fusion-based neutron generators can provide production rates around $10^{10} \text{ n}\cdot\text{s}^{-1}$; what would not be enough for treatment purposes. However, the characteristics of the generators allow for simultaneously using several units, in a

modular assemblies, increasing the net generation rates. In addition, generations of 10^{11} n·s⁻¹ are expected to be obtainable in a near future, what would help reaching the desired fluxes. Alternatively, the arrangements considered in the above mentioned designs can be adapted to other types of compact fusion-based neutron generators. Consequently, large enough neutron fluxes could be obtained that would be useful for several BNCT-related irradiations and, eventually, for clinical practice.

PS1 P 20

Effectiveness of epithermal neutron beam and neutron radiation shielding of samples in BNCT experiments

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The Boron Neutron Capture Therapy (BNCT) is one of the few methods for a treatment of the most severe brain tumors (e.g. Glioblastoma multiforme). Unfortunately, its usability is still limited by several drawbacks. The main problem is to find a suitable chemical compound, which would deposit selectively inside cancer cells and would not be toxic for healthy tissue. The research reactor LVR-15 (Rez, Czech Republic) participates in this field of research. The reactor is equipped with the special facility for BNCT research, which consists of a horizontal beam of epithermal neutrons, an irradiation room with accessories, and a beam operation room. In the past, even clinical study with human patients was realized, but only a basic research is still performed, nowadays. The biological effects of different boron compounds (respective their distribution in brain) are tested on the 6-days old sewer rats. Regrettably, irradiated sewer rats usually died a very short time after the end of irradiation, probably as a result of high radiation dose which was received by a whole body. Therefore, special protective cylinders were designed to reduce the unnecessary radiation (mainly from the gamma and neutrons). These protective cylinders should protect the body of a rat while leave its head unshielded. Two construction materials were considered – boron (in the form of boron carbide) and cadmium. In this contribution, suitable materials were tested by measuring of radiation characteristics inside the shielding. Neutron and gamma shielding parameters were measured by activation detectors and thermo luminescent detectors. As a result of measurement, boron carbide was found to be a better choice due to its ability to absorb neutrons without production of high energy gamma radiation.

PS1 P 21

Alanine Dosimeter Response Characteristics for Charged Particles in BNCT

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Introduction

In therapeutic irradiation field of BNCT, a variety of radiation (charged particles, neutrons, and γ -rays) are generated. These radiations which have various energies and cause various interactions, result in different biological effect. At

present, the dosimetry for BNCT was performed by indirect method, multiplying physical absorbed dose of charged particles or photons estimated by physical measurement by the values of RBE determined by biological experiment.

Alanine dosimetry is based on quantitative measurement of a radiation-induced free radical using Electron Spin Resonance (ESR) spectroscopy. It is known that the amount of chemical product induced by radiations is affected by radiation quality as biological effect. The purpose of this work is to develop more direct method of radiation quality evaluation using the alanine dosimeter, in which the LET and the RBE are taken into consideration. Their response characteristics of alanine dosimeter to charged particles of H, He, Li and C ions produced in BNCT was studied.

Materials and Methods

The dosimeters used in this study were BioMax of Eastman Kodak Company and Aminogray of Hitachi Cable, Ltd. The alanine thin film and rod dosimeters have sensitive layer composed of polycrystalline L- α alanine and binder. The dosimeters were irradiated with a few MeV various projectile ions. The ions were obtained from the Pelletron Van de Graaff accelerator at the Quantum Science and Engineering Center of Kyoto University. Absorbed dose to the dosimeters were calculated from beam size measurements by polyimide film and beam current measurements during irradiation.

The ESR measurements were performed at room temperature using JEOL JES-TE200 spectrometer operating at the X-band microwave frequency (9.43 GHz). The ESR spectrum was acquired with a modulation amplitude of magnetic field of 1.25 mT and a microwave power of 2.0 mW. The first derivative of the ESR absorption spectrum was recorded and the peak-to-peak amplitude of the central absorption line was measured as the dosimetric parameter.

Results

The ESR-dose response of the alanine dosimeter, which is proportional to the amount of free radical, is linear for doses between 10^2 - 10^4 Gy. ESR response per unit weight of irradiated alanine decrease with increasing the LET. Furthermore, it becomes constant in the high LET region (above 100 keV/ μ m). A high-LET radiation induces localized energy deposition near its trajectory, leading to a high ionization density. In this track region, enhancement of recombination or destruction of free radicals may occur. The result shows that the alanine dosimeter response is affected significantly by the radiation quantity such as the LET. It is known that RBE depends on LET, thus the alanine dosimeter response may show the difference of RBE of each ion.

Conclusion

This work indicates that alanine dosimetry provides useful information about the absorbed dose depending on the LET or RBE. Alanine dosimetry in BNCT may be performed biologically and directly with consideration for these important information.

PS1 P 22

Neutron Spectra Measurements at the research reactor TRIGA Mainz

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Neutron spectrometry using activation foils of different materials is a well-known method in BNCT¹. Each material has a characteristic energy dependent neutron capture cross section. The induced radioactivity is therefore proportional to the neutron flux of the energy range with high sensitivity. A spectrum can be reconstructed by irradiation of multiple foils.

Foils chosen were Copper, Gold, Indium, Manganese and Wolfram. They had a thickness of 12.5 µm, minimising self-absorption effects. They have been irradiated with and without cadmium cover in the research reactor TRIGA Mainz, Germany. Various positions have been examined, including the thermal column used for BNCT experiments, and in-core positions, mainly used for Neutron Activation Analysis (NAA). Foils were analysed using a standard high-purity germanium (HPGe) gamma spectrometry system (Canberra/GenieTM). Reconstruction of the spectra has been performed with the SAND-II algorithm², the needed a-priori spectra were calculated using MCNP-5³.

Resulting spectra will be shown for all positions and different experimental setups. Comparison of the positions shows the expected trends. With increasing distance to the centre of the reactor core neutrons are thermalized, while the integrated flux is reduced. Results are used for validation of existing Monte Carlo models and improvement of NAA applications.

[¹] D.W. Nigg, Physical Dosimetry and Spectral Characterization of Neutron Sources for Neutron Capture Therapy, in *Neutron Capture Therapy – Principles and Applications*, edited by W.A.G. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa (Springer-Verlag, Berlin Heidelberg, 2012), pp. 227-257.

[²] S. Berg, W.N. McElroy, *A computer-automated iterative method for neutron flux spectra determination by foil activation, SANDII (spectrumanalysis by neutron detectors II) and associated codes*, (1967).

[³] X-5 Monte Carlo Team, *MCNP: A General Monte Carlo N-Particle Transport Code*, Version 5, LA-UR-03-1987, Los Alamos National Laboratory (2003).

PS1 P 23

Fricke gel, electron spin resonance and thermoluminescence for integration and inter-comparison of measurements in NCT dosimetry

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In this work we investigated the potentiality of NCT dosimetry methods at the nuclear research reactor present in Řež (Czech Republic) through various kinds of techniques. In particular, we used three experimental techniques: Fricke gel dosimetry which allows to obtain 2D information about the various dose components by measuring the optical absorption induced by irradiation, electron spin resonance (ESR) dosimetry which provides information on neutron irradiation by measuring the concentration of free radicals induced by exposure, and thermoluminescence detectors with which it is possible to achieve mappings of gamma dose and of thermal neutron fluence.

Fricke-gel dosimeters allow achieving images and profiles of the various components of the absorbed dose in NCT. The method is based on suitably designed Fricke-gel dosimeters and the discrimination of dose components is achieved by means of pixel-to-pixel manipulations of light transmittance images obtained with gel-dosimeters having different isotopic composition. ¹⁰B can be added to the standard solution to achieve evaluation of boron dose and of thermal neutron flux. Heavy-water-gel can be used to separate fast neutron dose contribution.

Regarding electron spin resonance, experiments were carried out with two typologies of dosimeters composed of alanine and alanine added with boric acid (50 % by weight). The choice of ¹⁰B as additive nuclei is due to its very high capture cross section to thermal neutrons. The addition of boric acid increases the sensitivity of alanine pellets to thermal neutrons of about a factor 3. This sensitivity improvement has been exploited in this work to evaluate the thermal neutron components of the complex beam present at the reactor column used.

Lithium dosimeters LiF:MgTi containing different percentage of the isotope ⁶Li were exploited for measurements in the same phantoms: TDL-700, TLD-100 and TLD-600. In such phosphors, thermal neutron reactions with ⁶Li produce charged particles that release all their energy in the dosimeter. The small amount of ⁶Li unavoidably contained in TLD-700 detectors leads to a non-negligible contribution of thermal neutrons in the response of such TLDs. This contribution must be subtracted if these phosphors are used to measure the gamma dose.

For whichever chosen dosimeter, separation of dose contribution is necessary. Since the techniques used are complementary, the inter-comparison of the results obtained with these various methods is of great importance and provides valuable information to verify the correctness of the utilised separation procedures.

PS1 P 24

Dosimetric quantities measured by recombination chambers in low-energy neutron beams

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Radiation effects of BNCT are associated with four-dose-component radiation field - boron dose (from the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction), proton dose from the $^{14}\text{N}(n,p)^{14}\text{C}$ reaction, neutron dose (mainly fast and epithermal neutrons) and gamma-ray dose (external and from the capture reaction $^1\text{H}(n,\gamma)^2\text{D}$). The secondary charged particles generated in tissue have an LET spectrum resulting from the beam composition and therefore a microdosimetric characterization of the beam can be useful for monitoring of its quality and of possible variations with time. Such method is not in routine use, mostly because typical microdosimetric instruments like TEPC counters cannot be used in therapeutic beams of high dose rate. Other instruments that can be used for this purpose are parallel plate recombination ionization chambers, which are known as reliable detectors for determination of gamma and high-LET dose components and for characterization of radiation quality of mixed radiation fields. Specially designed recombination chambers can operate correctly even at high dose rates of therapeutic beams, and can be used for determination of dose versus LET distribution $D(L)$, however their resolution, in terms of $D(L)$ spectrum, is much lower than the resolution of the TEPC counters.

Earlier investigations, performed in nuclear reactor beams, including the BNCT beam of Research Centre Rez (Czech Republic) confirmed that a set of specially designed recombination chambers make it possible to determine total absorbed dose, dose components and few other dosimetric quantities, which are complementary to routinely used ones. Our set of recombination chambers includes a TE chamber and three non-hydrogen (graphite or titanium) chambers filled with different gases – CO_2 , N_2 and $^{10}\text{BF}_3$, in order to determine the absorbed dose components due to thermal neutrons, ^{14}N capture, gamma, and fast neutron. The separation of the dose components was based on differences of the shape of the saturation curve, in dependence on LET spectrum of the investigated radiation. New user-friendly software has been elaborated for this purpose.

The most important advantage of the recombination chamber is their ability to measure the above mentioned dose components directly in the beam and there is also no need for determination of neutron spectrum. The full set of the chambers can be used for characterization of the beam, especially in comparison with other measurements. The TE chamber can be also used for *on-line* monitoring of the absorbed dose rate. For this purpose the wall thickness can be adjusted by appropriate cups, or the chamber can be placed in a water phantom. The same chamber, or the second one of the same type, can be used for monitoring of the dose composition by continuous measuring of recombination index of beam quality, R_Q which is a simple function of the measured amount of ion recombination at a specially chosen polarizing voltage. The value of R_Q depends on both relative contribution of gamma radiation to the absorbed dose and on neutron energy. Therefore, its use in the beam monitoring can become of special interest in accelerator based BNCT beams.

The paper shortly summarizes the measuring methods and presents examples of the measuring results.

PS1 P 25

Dosimetric quantities measured by recombination chambers in low-energy neutron beams

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Radiation effects of BNCT are associated with four-dose-component radiation field - boron dose (from the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction), proton dose from the $^{14}\text{N}(n,p)^{14}\text{C}$ reaction, neutron dose (mainly fast and epithermal neutrons) and gamma-ray dose (external and from the capture reaction $^1\text{H}(n,\gamma)^2\text{D}$). The secondary charged particles generated in tissue have an LET spectrum resulting from the beam composition and therefore a microdosimetric characterization of the beam can be useful for monitoring of its quality and of possible variations with time. Such method is not in routine use, mostly because typical microdosimetric instruments like TEPC counters cannot be used in therapeutic beams of high dose rate. Other instruments that can be used for this purpose are parallel plate recombination ionization chambers, which are known as reliable detectors for determination of gamma and high-LET dose components and for characterization of radiation quality of mixed radiation fields. Specially designed recombination chambers can operate correctly even at high dose rates of therapeutic beams, and can be used for determination of dose versus LET distribution $D(L)$, however their resolution, in terms of $D(L)$ spectrum, is much lower than the resolution of the TEPC counters.

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The paper shortly summarizes the measuring methods and presents examples of the measuring results.

PS1 P 26

Evaluation of TLD 600/700 responses at different irradiation fieldsT. A. Cavalieri, V. A. Castro, P.T.D. Siqueira

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The implementation of a gamma dosimetry system based on TLD 600/700 pair has been attained by the BNCT research group of Ipen, in order to cope with international standard procedures, replacing the so far procedure which lays on TLD 400 measurements. The intended procedure was carried out by the response study of all mentioned TLDs to different radiation fields of increasingly complexity, before using them at the BNCT research facility. The radiation fields used in this work were:

- (1) a pure gamma field, derived from a 10 mCi ^{60}Co calibration source;
- (2) a mixed neutron-gamma field driven from a 2 Ci AmBe source placed inside a polyethylene moderator arrangement and
- (3) a mixed neutron-gamma field driven from IPEN/MB-01, a bench marked zero power reactor.

Besides presenting fields with different intensities and compositions, the experimental parameters from all arrangements were known to an extent so that simulations could be done with great accuracy. Simulations with the MCNP code were run in parallel to the experiments and provided not only discrimination of the field's components but also their contribution to the dose delivered to each one of the TLDs from each single field component.

The adopted working procedure provided a better understanding of the responses of each type of TLDs to gamma and thermal, epithermal and rapid neutrons. TLD 400 in spite of been insensitive to neutrons, has not shown a so good precision as TLD 600 and TLD 700 do. TLD 600 has shown a marked relationship between the two dosimetric areas under the glow curve and relative intensities of gamma and thermal neutrons. TLD 700, on its turn, has shown to be sensitive to neutrons which may overestimate gamma dose. The TLD 600/700 pair may therefore be used to performed mixed beam dosimetry but demand a clear understanding of its limitations mainly in a not negligible epithermal neutron field, which is the present case of the BNCT research facility at Ipen.

PS1 P 27

Dosimetry of Mainz reactors by means of ESR dosimetry with alanine added with gadoliniumM. Marrale¹, T. Schmitz², G. Hampel², M. Brai¹, A. Longo¹, S. Panzeca¹, S. Gallo¹, L. Tranchina³

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Neutron Capture Therapy (NCT) has found to be promising for treatments of tumours which hardly can be treated with other techniques such as gliomas. Alongside with the improvements of this technique, the development of techniques for the beam characterization arouses great interest in order to optimize the therapy procedures by reliably determining the various (neutronic and photonic) components of the mixed beam usually employed for therapy.

In the last years there is a large interest in alanine Electron Spin Resonance (ESR) dosimetry for electron and photon beams. Furthermore, recently the applications of ESR dosimetry for high LET radiation beams such as carbon ions and neutrons are continuously increasing. This is because of the very good dosimetric features of alanine EPR detectors such as: tissue equivalence, linearity of its dose-response over a wide range, high stability of radiation induced free radicals, no destructive read-out procedure, no sample treatment before EPR signal measurement and low cost of the dosimeters. Moreover, in order to improve the sensitivity to thermal neutrons of alanine dosimeters the addition of additive nuclei such as gadolinium acid was previously studied. The choice of Gd as additive nucleus is due to its very high capture cross section to thermal neutrons and to the possibility for secondary particles produced after interaction with thermal neutrons of releasing their energy in the neighbourhood of the reaction site. In particular, it was found that low concentration (*i.e.* 5% by weight) of gadolinium oxide brings about a neutron sensitivity enhancement of more than 10 times without heavily reducing tissue equivalence.

In this work we have studied the response of alanine pellets with and without gadolinium exposed to the thermal column of the Mainz reactor. Pure alanine dosimeters used were produced by Synergy Health (Germany) whereas the Gd-added dosimeters were produced at the University for Palermo. The irradiations were performed inside polyethylene holders to guarantee charged particle equilibrium conditions. ESR measurements were carried out through Bruker ECS106 spectrometer equipped with a TE₁₀₂ rectangular cavity.

The results of ESR experiments are compared to Monte Carlo simulations aimed at obtaining information about the contribution of the various (neutronic and photonic) components to the total dose measured by means of ESR dosimeters.

PS1 P 28

Extension of the alpha spectrometry technique for boron measurements in bone

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Introduction

In this work, the possibility of extending the technique of Alpha spectrometry to determine the boron concentration in Osteosarcoma and healthy bone is explored.

The charged particle spectrometry developed at University of Pavia [S. Bortolussi, S. Altieri 2013] allows boron concentration measurements in thin tissue sections. This technique was validated experimentally in the particular case of soft tissue. For hard tissues such as bone, generating thin samples represents an important technical issue since their structural characteristics limit the application of sectioning methods by cryostat.

A known approach to alter the bone structure so that it can be cut with conventional cryostat is chemical decalcification. This kind of aggressive treatments can modify the original boron concentration in samples. Therefore, a study is proposed to determine the appropriate procedure to generate the required samples minimizing boron loss. Another requirement of alpha spectrometry technique is the stopping power of alpha particles in the tissue of interest. Given that simulation by SRIM cannot reproduce with enough precision the nature of the samples, experimental measurements of stopping power in bone are performed.

Materials and Methods

Compact and spongy bone samples from sheep subjected to a BPA biodistribution protocol (i.v. 350 mg/kg, 45 minutes infusion) were obtained. Four decalcifying protocols were tested immersing the samples in: (a) EDTA (0.5M) and NaOH (pH ~ 8.5), (b) Hydrochloric acid (1.85%) and formic acid (4.75%), (c) nitric acid (6.5%) and (d) nitric acid (7.5%) and Formaldehyde (5%). For the first protocol, characterized by a slow decalcifying process, three samples of each type of tissue were immersed in EDTA disodium for one, two and three weeks, respectively. For the others, characterized by fast kinetics, one sample for each tissue was immersed for 24 hours. A compact and a spongy non-treated bone samples were used as control. During the experiment, the consistency of the samples was measured and the immersion time suitable for cryostat processing was assessed. Portions of the decalcified and control samples were digested in 30% nitric acid solution to measure the boron and calcium concentration by ICP-OES. The supernatant was also measured by HPLC in order to verify the presence of boron in the solution.

A transmission experiment was performed to determine the stopping power of alpha particles in sections of different thickness of compact bone (between 30 and 70 μm) decalcified in EDTA disodium for three weeks. A set-up consisting of a ^{241}Am source, a sample holder and a silicon solid-state detector was used to measure the residual energy spectra of the transmitted alpha particles.

Results and Conclusions

The optimal time of decalcifying process was assessed for each of the tested protocols. For compact bone, the best results were obtained after 3 weeks for protocol (a), 24 hours for protocols (b) and (d) and 42 hours for protocol (c). For spongy bone the optimal immersion time was 2 weeks for protocol (a), 24 hours for protocols (b) and (d) and 42 hours for protocol (d). The compact bone samples treated with EDTA for 3 weeks show a texture very suitable for cryostat processing and the obtained sections do not need support for the transmission experiments. On the contrary, the spongy bone samples are very fragile and they must be deposited on a solid support to be measured, analogously to soft tissues. HPLC measurements confirmed the presence of non-negligible BPA concentrations in all the decalcifying solutions. Final quantification of boron and calcium retained in samples is underway.

A curve of residual energy as a function of the thickness of compact bone tissue was obtained. According to the results on the boron loss measurements, the most

suitable technique of sample preparation will be selected for alpha spectrometry experiments.

PS1 P 29

Characteristics and Application of a Spherical Type Activation-based Detector for Neutron Spectrum Measurements at the THOR BNCT Facility

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Neutron spectrum measurements based on multiple foils activation are a common practice in reactor dosimetry and neutron beam characterization. The passive activation detectors prevent from complex dead-time correction when using in an intense neutron field, such as those beam designs for born neutron capture therapy (BNCT). A spherical type activation-based detector was developed aiming to measure the BNCT epithermal neutron beam at Tsing Hua open-pool reactor (THOR). The activation foil holder designed in a spherical shape can minimize the effect of neutron angular distribution and offer possibilities to modify the detector response function for the spectrum unfolding purpose by introducing moderators, absorbers, filters to the embedded foil. In addition to multiple activation foils, the detector can have various configurations by combining different materials of moderators, absorbers, and filters to create a rich set of response matrix that can improve the quality of unfolded spectra.

The response functions of various detector configurations were calculated using the Monte Carlo transport code MCNP5 version 1.61 with the ENDF/B-VII.0 cross-section library. The generated response functions had 640-group structure to facilitate the spectrum unfolding using the SAND-EX code, which uses the same unfolding algorithm as the well-known SAND-II and offers several additional features. This paper presents the design of the detector, important characteristics of the response functions for various detector configurations, and its application to neutron spectrum measurements at the THOR BNCT facility. The measured spectrum was compared with that determined previously based on the standard foil activation method. The advantages and limitations of the detector were evaluated and discussed.

PS1 P 30

PGNAA system preliminary design and measurement of IHNI

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Abstract

Recently develop a prompt gamma activation analysis (PGNAA) facility at Beijing at the 30kW research reactor in the Beijing Capture Technology Limited Co. The neutron flux of the special designed thermal neutron beam was used. The

characteristic of the beam was measure. The thermal flux of the beam is $3E06 \text{ n.cm}^{-2}.\text{s}^{-1}$. The PGNA system is composed by a large single n-type HPGe detector of 40 % efficiency, digital spectrometer and shielding part. For both detector shielding part and the neutron beam shielding part, the inner layer was natural LiF powder and the outer is lead. The detection limits were obtained for boron in blood, which is 1 ppm, with 2 mL the sample volume.

Pa P2 01

Liquid Li based neutron source for BNCT and science application

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An accelerator based neutron source is important for BNCT and scientific applications. Lithium (Li) is a suitable target material to generate low energy neutrons through ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction. Owing to lower energy nature of neutron generation, this system produces less gamma-ray in moderator and shield. In our design, Li target consists of liquid metal free surface flow in vacuum with high beam power removal capability. Lower beam energy allows us to employ electrostatic beam equipment. Neutrons of $\sim 10^{13} \text{ n/sec}$ will be generated with a beam current of 30 mA at around 2.5 MeV, corresponding to the energy of the first resonance of the reaction. As for collimator/moderator, polyethylene including boron and lead were used for neutron and gamma-ray shield, respectively. Neutrons were moderated with a pair of material having different moderation performance made of light and medium density material.

In 2013, after careful estimation on the basic design performance, experiments were carried out with using a dynamitron accelerator in Birmingham University with exported test equipments from Japan. As a result of the experiment, it was found that the neutron flux was collimated as designed by numerical calculation, and that gamma ray dose for a human body could be suppressed to a similar level to those at research reactors.

In the present design, Li target flows in a horizontal channel and beams come vertically downwards. Neutrons are transported vertically and a patient is placed on a bed below the collimator. The switching ON and OFF of the beam is so easy and quick that simple interlocks of the beam will secure patients and practitioners from radiation exposures and high voltage hazards. Since the lithium flow is contained in a vacuum channel covered with an additional wall and a thick radiation shield, containment of Li is very secure. The facility is constructed on an area of 17m x 17m with an electric demand of approximately 0.5MVA.

This facility will be constructed in two years, followed by commissioning and inspections for a year. After the completion pre-clinical experiments will be initiated by researchers of the dental surgery and cranial nerve surgery of the University.

In addition to this report, three presentations on the mock-up experiment and the experimental results on gamma-ray and neutron measurements are presented in the conference.

Pa P2 02

Study on the accelerator-based neutron source using Be(p,n) reaction with proton energy of lower than 30 MeV

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At Kyoto University Research Reactor Institute (KURRI), over 470 clinical studies have been performed as of March, 2014. On the other hand, cyclotron-based epithermal neutron source (C-BENS) was developed and installed in KURRI. Clinical trials for recurrent malignant glioma using C-BENS were started on October, 2012. C-BENS has good property for boron neutron capture therapy such as higher epithermal neutron flux, lower fast neutron and gamma ray contamination than Kyoto University Research Reactor (KUR). In order to prevent the blistering on beryllium target, proton energy of 30 MeV was selected. Protons penetrate beryllium target and inject to cooling water located behind beryllium target. In the future, if the blistering will be overcome using some technologies such as new hydrogen storing alloy as backing materials, it is important and meaningful to design accelerator-based neutron source using Be(p,n) reaction with proton energy of lower than 30 MeV because it can be reduced the activation of system component. We optimized the moderator for the Be(p,n) reaction with typical proton energy of 16 MeV. The treatment beam properties and dose distribution in a water phantom were shown in this presentation.

The moderator was optimized using the Monte Carlo simulation code of MCNPX and nuclear data of ENDF/B-VII for neutron production reaction at beryllium target. Figure of merits of the optimization are the contamination of fast neutron and gamma ray in free air condition, intensity of epithermal neutron flux, characteristics in water phantom. In order to evaluate the dose distribution in water phantom, calculation factors such as boron concentration and the boron concentration ratio of tumor to brain were assumed to be 25 ppm and 3.5, respectively. The irradiation time was determined by the limit of the peak brain dose of 10Gy-eq. The depth at 10Gy-eq and 25 Gy-eq of tumor dose were called Advantage Depth (AD) and AD25, respectively.

The moderator consists of iron, aluminium, and calcium fluoride. Iron works as a moderator material because of having nuclear reaction of inelastic scattering over 1 MeV. Aluminium has the valley of cross section at the energy of 27 keV and 100 keV. Neutron energy of 100 keV is high to use as treatment beam. Epithermal neutrons with the energy around 27 keV penetrate the material of aluminium and calcium fluoride because fluorine has the resonance cross section at 100 keV. Some researchers use magnesium fluoride as filter instead of the combination of aluminium and calcium fluoride. Neutron spectrum and fast neutron contamination (around 2.4×10^{-13} (Gy/cm²)) of the combination of aluminium and calcium fluoride is harder and larger than that of magnesium fluoride. However, AD and AD25 of 9.0 cm and 6.5 cm, respectively, of the combination of aluminium and calcium fluoride are longer than that of magnesium fluoride.

Epithermal neutron flux per proton current of 1 mA for the combination of aluminium and calcium fluoride was 5.5×10^8 (n/cm²/s) and irradiation time was estimated to 86 minutes.

We optimized the moderator using Be(p,n) reaction with the proton energy of 16 MeV. Epithermal neutron flux of 10^9 (n/cm²/s) will be obtained using the proton current of 1.8 mA. It was found that the treatment beam property and dose distribution in a water phantom was better than that of C-BENS. If the blistering will be overcome, this system can be applied to BNCT clinical studies.

Pa P2 03

Experiments and simulations using a high flux DD neutron generator

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Common sources for generating the neutrons needed for patient treatment are nuclear reactors, expensive accelerator facilities or radioactive isotopes. Less expensive and more compact neutron sources can be achieved by using the DD and DT fusion reactions, which produce fast neutrons that must be moderated. However, calculations by others show that for single beam geometries, one must start with large fast-neutron yields of $> 10^{13}$ n/s to achieve adequate thermal fluxes at the tumor site. Our MCNP calculations show that we can reduce this required fast neutron yield by roughly an order of magnitude by using multiple DD neutron generators and a cylindrical moderator that surrounds the patient. A four beam neutron source with an internal moderator has been constructed at Adelphi Technology that tests some of the technical issues of producing such a device. The generator is in the process of being tested and is expected to produce thermal (<0.5 eV) neutron fluxes of $0.5 - 1 \times 10^8$ neutrons/(cm²-sec) which are comparable to those achieved in a nuclear reactor. This flux is achieved using four ion beams arranged concentrically around a target chamber containing a compact moderator with a central sample cylinder. Fast neutron yield of $\sim 2 \times 10^{10}$ n/s is created at the titanium surface of the target chamber. The thickness and material of the moderator is selected to maximize the thermal neutron flux at the center. This generator is designed for neutron activation analysis and radioisotope production, thus the sample area is fairly small. For BNCT research the generator could be suitable for small animal testing. The DD110MB provides us a tool to improve and benchmark our simulation design for larger systems. The DD110MB also proves the feasibility of running multiple neutron generators heads from one control electronics and power supply rack. Compared to some other methods of producing neutrons, the DD110MB does not use radioactive materials but instead the deuterium-deuterium fusion reaction. Thus a minimal amount of unwanted activation and radiation is produced. This provides reduced administrative and safety requirements.

Pa P2 04

Neutron Generator for BNCT Based on High Current ECR Ion Source with Gyrotron Plasma Heating

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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 for.

A so-called high current quasi-gasdynamic ECR ion source with plasma heating by millimeter wave gyrotron radiation is suggested to be used in a scheme of D-D neutron generator in the present work. Ion source of that type was developed in the Institute of Applied Physics of Russian Academy of Sciences (Nizhny Novgorod, Russia). It can produce deuteron ion beams with current density up to 700-800 mA/cm². Generation of the neutron flux with density at the level of 7-8·10¹⁰ s⁻¹cm⁻² could be obtained in case of TiD₂ target bombardment with deuteron beam accelerated to 100 keV. Estimations show that it is enough for formation of epithermal neutron flux with density higher than 10⁹ s⁻¹cm⁻² suitable for BNCT. Important advantage of described approach is absence of Tritium in the scheme.

First experiments performed in pulsed regime with 300 mA, 45 kV deuteron beam directed to TiD₂ target demonstrated 10⁹ s⁻¹ neutron flux. This value corresponds to theoretical estimations and proofs prospects of neutron generator development based on high current quasi-gasdynamic ECR ion source.

Pa P2 05

Design and simulation of an optimized photoconverter for e-linac based neutron source for BNCT research

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In the past years, interesting results have been obtained using as a neutron source for BNCT preclinical research the portable photoconverter prototype PhoNeS (Photo Neutron Source) coupled with commercial high energy e-linac's employed in hospital for cancer radiotherapy .

The main limit of this device was the maximum achievable thermal neutron flux of E7 n cm-2 s-1, corresponding to an irradiation time of biological samples of about 3 hours.

At present, a new optimized photoconverter has been designed and simulated,

suitable to produce an iperthermal neutron field greater than $E8 \text{ n cm}^{-2} \text{ s}^{-1}$, if coupled with a dedicated e-linac in which the working parameters are modified, to maximize the neutron photoproduction.

By using MCNP-GN and GEANT4 MC simulation codes, an accurate study of material composition and geometry of the photoconverter has been carried out, to moderate the photoneutrons produced by GDR reaction in the high Z core until thermal/epithermal energies, with low contamination of fast neutrons and photons.

The transport of neutron inside a simplified anthropomorphic phantom (Jimmy), with holes corresponding to critical organs placed according to ICRP60 recommendations, has been evaluated and the BNCT physical dose at the organs is calculated in various irradiation conditions.

The results confirm the interest in employing modified commercial high energy e-linac, coupled with suitable photoconverters, as in-hospital neutron sources for research in BNCT.

On the base of this study, it should be possible in the future to design and realize a new especially designed high energy electron linear accelerator, to achieve the neutron flux required for clinical BNCT.

Pa BI1 01

Detection of cellular boron in human glioblastoma biopsies after infusion of BPA

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Measurement of the microscopic spatial distribution of boron in target tissue allows for, among other uses, validation of its specific cellular uptake and delivery following administration. Here we have measured, using secondary ion mass spectrometry (SIMS) and induction coupled plasma mass spectrometry (ICP-MS), the trans-cellular distribution and abundance and bulk levels of boron in glioblastoma-derived biopsies of patients infused with a mannitol formulation of BPA.

Patients with a presumptive diagnosis of glioblastoma WHO grade IV and who were enrolled into our CRUK-funded pharmacokinetic study were variously infused with BPA prior to undergoing biopsy surgery. Stereotactic needle biopsies of tumour and brain-around-tumour (BAT) tissue taken at 2-3 h post-infusion were imprinted within 1 min of removal onto silicon substrata which were then snap-frozen in liquid nitrogen-chilled slurry of isopentane. To minimise any chemical redistribution samples were stored at -80°C before introduction into the high vacuum SIMS instrument. Boron was measured with a BioToF SIMS instrument fitted with a 20keV Au^+ liquid metal ion source at a sample current of 1.7 nA and focused probe size of $\sim 1 \text{ m}$ in etched areas of the imprints; K^+ , Na^+

and C⁺ were measured simultaneously to confirm tissue presence and integrity. Ions were quantified in the 256 x 256 pixel spatially-resolved isotopic images with standard image analysis software. Gross boron levels were measured in adjacent biopsies with ICP-MS.

When discernable, cell boundaries or cell clusters were identifiable as aggregates of K⁺ ions bounded by a ring of Na⁺ ions, thus signifying chemical integrity. Boron was distributed extra- and intra-cellularly. Its undivided ratio of abundance, measured by SIMS and normalised to C⁺, in tumour vs BAT tissue was 0.96, 1.85 and 2.40 in intravenous, intravenous+mannitol bolus, and intracarotid cohorts of BPA infusion respectively at ~2h after end of infusion (n=3 per cohort). The corresponding ICP-MS values were 1.78, 1.36 and 2.50. These data demonstrate tissue specific and targeted delivery of boron with BPA-mannitol in glioma patients and suggest that intra-arterial infusion may be a more effective route of delivery for glioblastoma.

Pa BI1 02

A method for individual quantitation of the combined boronophenylalanine and borocaptate by liquid chromatography-electrospray ionization-mass spectrometry

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In clinical trial of boron neutron capture therapy (BNCT), two boron compounds enriched with ¹⁰B, sodium borocaptate (BSH) and *p*-boronophenylalanine (BPA) have been used as the drug-targeted binary radiotherapy. It has been reported that BSH, as a thiol-containing hydrophilic compound with higher boron content and reaction efficiency to neutron, could be incorporated into the brain tumors. However, the weak ability to penetrate cell membrane and lower selectivity to tumor cell are also obstructed its application, simultaneously. In order to improve the drug effectiveness, especially for the requirement of malignant brain tumors in BNCT clinical trial, it is reasonable to use BSH in conjunction with BPA, known as a phenylalanine analog for accumulated actively in the tumors but verified to be a heterogeneous distribution and incorporated partly into normal tissues. Although total ¹⁰B concentration from both of BSH and BPA accumulated in the tumor tissue or blood could be calculated by prompt gamma-ray spectrometry (PGA) or inductively coupled plasma (ICP) etc., it is disable to ascertain ¹⁰B origin. Herein, an analytical method to separate and determine ¹⁰B-enriched compound respectively from the different original boron compounds as BSH and BPA is proposed, and the applicability to blood samples are also studied.

As a precursor, ¹⁰B-BSH was dissolved into ultrapure water directly, and ¹⁰B-BPA was optimized for dissolution completely by using ultrasonication for 6h in the preliminary experiment. Both of the concentration for BSH and BPA are adjusted to 1000ppm as a stock solution. Subsequently, standard solution of [¹⁰B-BSH+¹⁰B-BPA] was mixed, and corresponding contents were diluted for measurement. The experiment is performed by means of high-performance liquid chromatography coupled with electrospray ionization-mass spectrometry (HPLC/MS). The mobile phase is selected as methanol loaded with 5mM DHAA(di-hexylammonium

acetate: an ion-pairing reagent), and the chromatography is performed by a Shim-pack FC-ODS column. Additionally, plasma separated from whole human blood was used to investigate applicability for blood samples.

As the results, BSH and BPA are separated completely according to the peaks appeared at different retention times on HPLC after loaded with ion-pairing reagent. It could be concluded that the longer alkyl chains of DHAA increase hydrophobicity of BSH to better separation for different boron compounds. The positive ion [$^{10}\text{B}_{12}\text{H}_{11}\text{SH}_3\text{C}_{12}\text{H}_{28}\text{N}$] $^+$ at m/z 723 for ^{10}B -BSH and the negative ion $[\text{M-H}]^-$ at m/z 207 for ^{10}B -BPA are identified from mass spectra and quantified by selected-ion monitoring chromatogram. Furthermore, the plasma mixed with $[\text{BSH}+\text{BPA}]$ was investigated in the same analytical condition for evaluating the applicability of blood samples. It is expected that this analytical method might contribute to clinical trial of BNCT because of possibility to radiation estimation for patient accepted, and to clarification of pharmacokinetic property from different boron-containing medicine.

Pa BI1 03

Development of rapid and precise boron isotope analysis in whole blood by HR-ICP-MS

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Precise and accurate measurements of boron concentration and isotope ratios in whole blood are important to determine the irradiation time in boron neutron capture therapy (BNCT), since accurate estimation of the blood boron level before irradiation is required. An analytical method has been developed to determine boron in whole blood samples by High-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) in this study.

Evaluating the validation of the isotopic ratio measurements using the method of mass bias correction by analyzing NIST SRM 1643e, good agreement was obtained between measured value and natural abundance of boron isotope ratio with a relative error of 0.35 %. Measuring boron concentration and isotope ratios in BPA solutions using the method of mass bias correction, accurate measured value was obtained under the condition that boron concentration was less than 0.5ppb.

Simulated plasma was used to confirm influence of matrix elements against the determination of boron. As a result, it was found that accurate measured value of boron concentration and isotope ratios could be obtained despite the presence of high concentration of matrix elements. Herewith, boron in whole blood could be measured without having to pass a separation and purification process.

Selecting appropriate pre-treatment is needed to prevent nebulizer from clogging and also prevent ion optics from being polluted due to the presence of

protein and electrolyte salt in whole blood sample. In order to find the optimum digestion method of whole blood sample, boron recovery test using microwave digestion method in closed system were performed. There is a possibility of boron analyte loss in the case of open system digestion due to the chemical property of boron volatility. The whole blood sample was digested in insert vessels (Teflon/Quartz) with addition of nitric acid and $B_4H_{10}N_2O_{11}$ /BPA/BSH solution. It took 45 min. (digestion time: 25 min. + cooling time: 20 min.) to complete the full treatment. Boron recovery was above 98% with low RSD. In terms of B isotope ratios of B solution, measured value was in good agreement with the natural abundance, as for BPA/BSH solutions, favorable B isotope ratios were obtained. From the above results, the microwave-assisted wet ashing/ HR-ICP-MS was applied for an accurate determination of boron in whole blood samples. In addition, PTFE vessel superior in operability and reproducibility was selected as the digestion vessel.

However, such developed methods are time-consuming for clinical BNCT. It is therefore necessary to develop more rapid and efficient method. We will investigate the rapid method for preventing boron analyte loss using hotplate digestion in closed system.

Pa BI1 04

Parameter optimization for the determination of BSH in whole blood by ¹⁰B-NMR

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Introduction

Tracking of chemical changes of boron chemical species is important in terms of pharmacokinetics study. Two traditional methods; PG-SPECT and ICP-AES could not determine concentrations of boron chemical species. On the other hand, we can determine boron concentrations of these boron compounds individually using ¹⁰B nuclear magnetic resonance spectroscopy (¹⁰B-NMR), because BPA, BPA-Fr, BSH, BSSH and boric acid show different signals on ¹⁰B-NMR. We have previously reported simultaneous determination of BPA and BPA-Fr in water and blood derivative using ¹⁰B-NMR. It was that quantitative performance and detection limit of ¹⁰B-NMR signals were significantly reduced in the whole blood samples due to the high viscosity. Recently, we have improved quantitative performance and detection limit on the ¹⁰B-NMR-determination of BSH in whole blood by the optimization of measurement conditions. In this report, the optimization of ¹⁰B-NMR measurement conditions (¹⁰B-NMR parameters) for the quantitative determination of BSH in whole blood is described.

Materials and methods

Deionized water was deoxidized by Ar bubbling and refluxing. All BSH samples were prepared in the N₂ glove box. A 50 ppm ¹⁰B BSH mother solution was diluted by adequate amounts of water or whole blood to give 5, 10, 15, 20, 25, 50 ppm ¹⁰B BSH sample solutions. NMR spectrometer was JEOL ECA500, and BF₃·OEt₂ with D₂O capillary was used for external reference ($\delta = 0$ ppm). Measurement conditions (scan number, x-points, pulse delay (P.D.), temperature and spinner) were firstly optimized until peak intensity and peak area of 20 ppm

^{10}B BSH sample in whole blood was improved. Next, ^{10}B -NMR spectra of 5-50 ppm ^{10}B of BSH in water or blood were measured under optimized conditions.

Results

Four peaks at $\delta = -17.0, -13.6, -11.4,$ and -7.1 ppm were observed in the water sample (20 ppm ^{10}B) those were assigned to *para*-, *meta*-, *ortho*-, and *ipso*-positioned boron of BSH respectively. The former three peaks were split into two by boron-hydrogen spin-spin coupling ($J_{\text{BH}} = 40\sim 47$ Hz). A few contaminated dimer peak was observed at $\delta = 4.3$. In the whole blood sample, two peaks those assigned to *ipso*- and *para*-positioned boron atoms were disappeared, and quantitative performance and detection limit were reduced due to the peak broadening. Under the optimized conditions (10 000 scans, $x = 2\ 048$ points, temp. = 55°C , spinner = 15 Hz and 30 ms of P.D.), BSH was detectable until 2 ppm ^{10}B . Because of peak broadening resolution and boron concentration could be measure quantitatively until 5 ppm ^{10}B .

Conclusion

We have successfully improved quantitative performance and detection limit on ^{10}B -NMR determination of BSH in whole blood. Present method would provide precise in vivo pharmacokinetics of BSH for BNCT.

Pa BI1 05

First observation of the complex of BPA with blood component in whole blood by ^{10}B -NMR

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Introduction

Boron part of BPA can make an anionic complex with monosaccharide, and one of the monosaccharide, fructose, is used as the BPA-fructose complex in BNCT to increase the solubility of BPA. Recently, we have reported the determination of BPA and BPA-complexes in Blood (red cell concentrates including mannitol, adenine, phosphate (RCC-MAP)) by ^{10}B -NMR. But, in actual BNCT, BPA is injected by intravenous drip. Therefore, the determination of the compounds in whole blood is important. In the developing of ^{10}B -NMR determination method in whole blood, we have found that BPA could complex with the blood components.

Materials and methods

NMR used was JEOL ECA500 with which ^{10}B auto-tuning system was equipped. Sample tube used was 5-mm Φ quartz tube. ^{10}B -NMR measurements were carried out without a sample spin and field lock. BF_3OEt_2 ether solution with D_2O capillary was used for external reference ($\delta=0$ ppm). Ninety degree pulse was used. The resonance frequency of ^{10}B is 53.735 MHz. Relaxation delay time was 30 msec (minimum value). Receiver gain was fixed as 60. x-offset was 30, x-sweep was 700 ppm. ^{10}B -NMR spectra were obtained by 100 000 times FT-accumulation scans. BPA was mixed with the whole blood of K. Yoshino, one of the authors. The concentration of BPA was 50 ppm as ^{10}B .

Results

^{10}B -NMR spectrum of this sample clearly showed the ^{10}B -NMR peak of the BPA

complex in addition to that of BPA. From the chemical shift of the peak, this signal seemed to be the monosaccharide such as glucose. This is the first evidence report of the interaction between BPA and the blood component. This enables us to study of BPA- accumulation in tumor.

Conclusion

Since the discovered complex was anionic compound (the reason will be presented in 16th ICNCT), the solubility of BPA would be increased by becoming BPA-blood compound complex. This means the amount of fructose can be decreased when one prepares the BPA-fructose solution in actual BNCT

Pa Ch2 01

Hyaluronic acid- and melanin-based boron compounds for combined neutron capture therapy

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Introduction

Functionalization of boron compounds can reduce excessive irradiation of healthy tissues and improve the results of therapy through active targeting of tumor cells. It is known that receptors to hyaluronic acid (HA) are widely present in tumor cells and especially gliomas, playing the role in tumor invasion. Due to their chemical structure, melanin molecules can imbibe a large number of active metal compounds, such as boron, providing its high concentration. Using nano-sized hydroxyapatite carriers for boron-hyaluronic acid (BHA) might improve boron accumulation in tumor cells. With the addition of gold, BHA-melanin-gold (BHA-MG) complexes might be used in the form of nanoparticles for combined neutron / photon capture therapy. We propose using HA, melanin, gold and hydroxyapatite to form a number of boron compounds for active tumor targeting and further combined neutron capture therapy. Depending on the viscosity of HA it might be possible to obtain boron compounds for parenteral and local use.

Materials and methods

We studied cytotoxicity and accumulation of boron compounds in vitro and in vivo. BHA, BHA-hydroxyapatite, boron-melanin and BHA-MG were produced by a solid-state synthesis and modification of polysaccharide-based polymers at the International research center "Martinex", Moscow, Russian Federation. We used C6 (rat glioma) and U251 (human glioma) cell lines and C6 rat glioma model. Size and form of nanoparticles were analyzed using JEM-1400 transmission electron microscope (JEOL Ltd., Tokyo, Japan). The cytotoxicity was evaluated with the MTS-assay (Cell Titer 96[®] AQueous One Solution, Promega, USA). Boron accumulation was measured using ICP-AES (ICP-8100, Shimadzu, Kyoto, Japan). The experiments were repeated thrice, the data represent means \pm SDs, and the p-values were calculated using one-way ANOVA.

Results and discussion

The studied compounds showed tolerable toxicity within therapeutic concentrations and different accumulation depending on their chemical and

physical properties. The biocompatibility might play the main role in the selection of certain types of compounds to be used in living organisms, and we suggest that toxicity might be connected with the presence of the compounds or their parts in ionized forms in the solution. HA is initially a non-toxic material present in many tissues in animals and humans, and the formation of the uniform layer of HA on the surface of nanoparticles might provide their low toxicity to biological systems. The rate of accumulation might be connected with certain capture mechanisms by tumor cells. When the molecule compounds, such as BHA, are suggested to attach to specific receptors on surface of tumor cells, nanoparticles are typically trap into cells by endocytosis, and we also suggest that both mechanisms might improve tumor targeting and prognosis of the therapy.

Conclusion

BHA, BHA-hydroxyapatite, boron-melanin and BHA-MG compounds showed tolerable toxicity, and the accumulation differed according to their physical and chemical properties. Further functionalization with the attachment of active molecules, such as complex polysaccharides or antibodies, might improve targeted delivery and therapeutic effect of the studied boron compounds. The current study is ongoing and final results will be presented at the congress.

Pa Ch2 02

Develop Boron-Containing Nanodiamonds for Boron Neutron Capture Therapy

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Drug delivery and drug targeting research in boron neutron capture therapy (BNCT) is essential and pressing. Zhu reported a delivery method connected $C_{2B_{10}}$ carborane cages and single-wall carbon nanotubes (SWCNTs) via nitrene cycloaddition.¹ However, there are several toxicity problems from structure, size distribution, surface charge and agglomeration of carbon nanotubes.² Our group provided the detonation nanodiamonds (NDs) as boron carriers in BNCT application. Detonation nanodiamonds exhibits biocompatibility and low toxicity, and is thus a promising candidate material for BNCT.³

The surface of detonation nanodiamonds was oxidized by concentrated nitric and sulfuric acid mixture formed carboxylic acid groups. After activation with thionyl chloride, they reacted with pinacol boronate ester (Bpin) as boron-containing molecules to form ester bonds conjugated onto surface of nanodiamonds. The boron-containing nanodiamonds (B-NDs) were evaluated by elemental analysis, X-ray photoelectron spectroscopy and boron ICP-mass. Also the B-NDs did not show significant cytotoxicity to normal cell line and may prospectively be applied in boron neutron capture therapy.

¹Zhu, Y.; Peng, A. T.; Carpenter, K.; Maguire, J. A.; Hosmane, N. S.; Takagaki, M. *Substituted Carborane-Appended Water-Soluble Single-Wall Carbon Nanotubes: New Approach to Boron Neutron Capture Therapy Drug Delivery*. *J. Am. Chem. Soc.* 2005, 127, 9875–9880. ²Kolosnjaj, J.; Szwarc, H.; Moussa, F. *Bio-Applications of Nanoparticles*; Chan, W. C. W., Eds.; Springer: Berlin, 2007; Vol. 620, pp 181–204.

³Krueger, A. *New Carbon Materials: Biological Applications of Functionalized Nanodiamond Materials*. *Chem. Eur. J.* 2008, 14, 1382–1390.

Pa Ch2 03

Boron containing magnetic nanoparticles for neutron capture therapy: An innovative approach for specifically targeting tumors

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Introduction

Focusing the therapeutic action in the tumor while sparing healthy tissues is always a precondition for a successful tumor therapy concept. Currently, a more effective boron delivery agent is highly desirable to perform successful BNCT drafts. A promising strategy to deliver boron into tumor tissues is using magnetically directed nanoparticles. In our previous work on *Magnetic Drug Targeting* (MDT) we achieved superior enrichment of superparamagnetic iron oxide nanoparticles (SPIONs) and bound chemotherapeutic agents in animal tumors of up to 415 ng/mg and a high selective (450-fold) tumor versus blood enrichment of SPIONs. In this study, we launched different experiments to merge BNCT and MDT concepts investigating the neutron flux behavior and biological outcome by irradiating three-dimensional cell-cultures.

Materials and methods

Experiments of the neutron beam behavior were performed at the prompt gamma activation analysis (PGAA) facility of the Forschungs-Neutronenquelle Heinz Maier-Leibnitz (FRM II) research reactor in Munich, Germany. The thermal neutron flux equivalent chosen for the measurements was 2.35×10^9 n/cm²s in air. This is appropriate to irradiate agarose gel (1.5 %) cubes for evaluating the irradiation of physiological tissues. For neutron flux density determination and dose calculations, the neutron flux attenuation was measured in dependence on the depth, concentration of the boron containing layer, co-presence of SPIONs in the boron-layer, co-presence of nitrogen and neutron beam attenuation behind bone material. Flux density was measured using the gold foil activation method. Magnetic boron containing nanoparticles have been prepared by precipitation and subsequent surface modification using carboranes. A three-dimensional cell-culture system derived from squamous cell carcinoma cells (VX2) was used to determine the biological outcome caused by irradiation. Therefore, tumor spheroids have been embedded inside the phantom structure at different positions. They were generated by sowing a suspension of a defined number of VX2 cells in an agarose-coated 96-well plate.

Results

Neutron flux density was hardly affected by boron (100-200 ppm), co-presence of SPIONs (15-300 µg/mg), co-presence of nitrogen in physiological concentrations (18-20 mg/g) or bone material. In comparison to pure agarose gels, nitrogen containing gels exhibits a 100-fold dose increase. Boron containment further increases the dose up to 1000-fold. PGAA and ICP-AES (plasma coupled atomic emission spectroscopy) revealed a boron payload of the SPIONs that is considerably above the required value of 4.8 % (m/m). Tumor spheroids mimic

tiny metastases and areas of solid tumors, and thus represent a more complex in vivo simulation for a variety of applications in tumor cell research. Histological processing of the before irradiated spheroids clearly monitored the biological outcome.

Conclusion

Our experimental setting resulted in the attempted concentration of the radiation doses in the targeted area and opens the opportunity for a successful combination of MDT and BNCT. The high linear energy transfer of BNCT in our experiments still prevails which is a precondition for further studies.

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Pa Ch2 04

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

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Introduction

The successful treatment of cancer by BNCT requires the selective delivery of large amounts of ^{10}B to tumor cells. *p*-borono-L-phenylalanine (L-BPA) has been widely employed as a ^{10}B agent in the clinical BNCT. While L-BPA accumulates into tumor cells spontaneously, it has some pharmaceutical drawbacks such as poor water-solubility (1.6 mg/mL) and a rapid decrease of ^{10}B concentration in tissue after administration. Therefore, a more effective ^{10}B carrier is required for making BNCT more successful.

In the present study, an attempt was made to formulate nanosuspension (NS) composed of L-BPA itself. The nano-sized L-BPA particles can be expected to be accumulated in tumor tissue more efficiently than the dissolved compounds (L-BPA-fructose complex, BPA-Fr) after intratumoral (i.t.) administration. The aim of this study is to develop the BPA-NS formulation and to investigate the effect of particle size of BPA-NS on biodistribution after its i.t. administration to tumor-bearing mice.

Materials and methods

L-BPA (^{10}B -enriched) was kindly supplied by Stella Pharma Corporation, Japan. Macrogol 15 hydroxystearate (Solutol[®] HS 15, SO) and soybean lecithin (SL) were used as stabilizers. BPA-NS using SO and SL (BPA-NS) was prepared by a wet-milling method with the use of a planetary ball mill (Pulverisette-7, Fritsch). By changing the operating conditions and the processing time, two types of BPA-NS with different mass median diameters ranging from 157 to 183 nm (NS200) and 358 to 402 nm (NS400) were prepared. Then the BPA-NS thus obtained was sonicated by a water-bath-typed sonicator (BRANSONIC[®] 2510J-DTH, Branson Ultrasonics Co.) for 5 minutes at room temperature.

Biodistribution of BPA-Fr, BPA-NS200 and BPA-NS400 was assessed using male B16F10 melanoma bearing C57BL/6J mice as an animal model with solid tumor. BPA-Fr and BPA-NSs (500 mg BPA/kg in dose) were i.t. administered to the melanoma-bearing mice under anaesthesia. At a predetermined time after administration, the mice were sacrificed and blood and tissue samples were collected immediately. Boron analysis for the samples was carried out by an ICP-AES method.

Results

I.t. administration of BPA-Fr was found to show a low boron accumulation in tumor; 6 hours after administration, ¹⁰B concentration was 29.2 ppm (11 % of boron accumulation of 5 minutes after administration) due to its rapid elimination from tumor. In contrast, when BPA-NS200 and NS400 were administered by the same manner as BPA-Fr, a quite high boron concentration in the tumor tissue was obtained, i.e., 108.7 ppm (61 %) in NS200 or 284.3 ppm (80 %) in NS400 even after 6 hours of administration. The significant effect of NS400 on ¹⁰B accumulation in the tumor was possibly due to the slower diffusion and/or dissolution of NS400 in the tumor.

Conclusion

The results demonstrated that BPA-NS having different particle sizes was effective to prolong and control the retention time of ¹⁰B in the tumor tissue with the significantly higher concentration, in comparison with BPA-Fr. By utilizing such unique characteristics as solid particles, i.t. administration of BPA-NS would show a potential ability to be used as a BNCT reagent showing tumor-selective, enhanced accumulation of ¹⁰B.

Tuesday June 17th 2014

Pa P3 01

Hyperion™ Accelerator Technology for Boron Neutron Capture Therapy

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The Li(p,n) reaction, which is widely considered to be the primary neutron producing reaction for use in accelerator-based Boron Neutron Capture Therapy (BNCT), requires proton accelerator technology that is capable of reliably producing a 20-30 mA proton beam with energy up to 2.5 MeV. This is well above the ion current limit of traditional DC ion accelerators. The compact Hyperion™ DC electrostatic accelerator developed at GT Advanced Technologies for applications in the semiconductor industry, is an innovative new approach to generation of high voltage, high current ion beams. The Hyperion™ is a single-ended ion accelerator that operates at proton current in the range of 40-50 mA and energy in the range of 2.0 – 2.5 MeV. It has voltage stability < 0.1% at full current, which is important for operation near the Li(p,n) reaction threshold. These parameters are very desirable for clinical application of BNCT. The high voltage generator is a gas pressurized high voltage DC system that employs two novel features. It uses a voltage generation technique based on stacked,

independently powered and independently controlled power supplies in place of simple diode rectifiers used in previous voltage multiplier high voltage generators.

Fiber optics is employed to control and monitor the series connected power supplies. The second novel design feature is the active stabilization of the acceleration tube gradient by attaching the output of each stacked power supply directly to the acceleration tube electrodes. This feature prevents fluctuations of the beam tube gradient, which are the primary cause of beam current limits in high current DC ion accelerators. These changes in voltage generation and architecture are engineered in a modular configuration that can readily be adapted to meet the demands of BNCT in a clinical environment. It also operates at very high electrical efficiency with a typical proton beam power to 'wall' power ratio of ~50 %. We present the major Hyperion™ design features and the operating conditions achieved to date.

Pa P3 02

High-Power Proton Irradiation and Neutron Production with a Liquid-Lithium Target for Accelerator-based BNCT

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A compact liquid-lithium jet target was bombarded for the first time with a high-intensity (~1.91 MeV, 1.3 mA, 2.5 kW) continuous-wave proton beam at Soreq Applied Research Accelerator Facility (SARAF). The experiments demonstrate the Liquid Lithium Target (LiLiT) capability to dissipate extremely high ion beam power densities (>0.5 MW/cm³) and constitute an intense source of epithermal neutrons, produced by the ⁷Li(p,n)⁷Be reaction, for Boron Neutron Capture Therapy (BNCT) in hospitals.

The liquid-lithium loop of LiLiT is generating a stable lithium jet at high velocity (up to 7 m/s) on a concave supporting wall, with free surface toward the incident proton beam. The liquid-lithium jet acts both as neutron-producing target and as a beam dump, by removing with the flow the thermal power generated by high-intensity proton beams (up to 10 kW). During proton irradiations the apparatus operated at a base temperature of ~200° C and a lithium flow velocity of ~2.5 m/s and experienced no significant change in temperature or vacuum.

With a proton beam irradiation of ~1.91 MeV energy, just above the ⁷Li(p,n) threshold of 1.880 keV, neutrons were continuously detected with a fission-chamber detector positioned at 0° with respect to the proton beam, while the intensity of the proton beam on the lithium target was monitored using the yield of γ rays, dominated by the inelastic ⁷Li(p,p' γ) reaction. Gold activation targets positioned in the forward direction show that the average neutron intensity during the experiment was ~2×10¹⁰ n/s.

A beam shaping assembly for BNCT with LiLiT, including polyethylene neutron moderator and a lead gamma shield, was designed based on Monte Carlo (MCNP) simulations of BNCT-doses produced in a phantom. According to these calculations it was found that a 15 mA proton current, (>1.91 MeV) will apply the therapeutic doses in a ~1 hour treatment duration, giving efficient therapy

for depth of up to ~4-5 cm. Based on the conditions of our LiLiT proton beam experiments, such high current beams can be dissipated in a liquid lithium target, provided a transverse radial Gaussian beam profile with a standard deviation in the range of 1.2 cm. Compact accelerators that can supply such proton beams (1.91 MeV, ~15 mA, $\sigma \approx \sim 1.2$ cm) are available, using up-to-date accelerator technologies.

The experimental irradiation of LiLiT with a high power proton beam at SARAF, along with the Monte Carlo simulations, demonstrate the feasibility of a full-scale accelerator-based BNCT neutron source based on a liquid-lithium jet target. The desired proton beam can be dissipated in a liquid lithium target, so in-hospital accelerator based BNCT with is within reach.

Pa P3 03

Development of a higher power cooling system for solid lithium targets

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The accelerator based BNCT beam at the University of Birmingham is based around a solid thick lithium target cooled by heavy water. This system was designed to provide an appropriate neutron spectrum for clinical BNCT, avoid problems with hydrogen blistering of the lithium and remain simple enough to potentially implement in a hospital environment. The current submerged impinging jet cooling system has been in routine use for more than 10 years and has been tested up to currents of 1.5 mA at 2.8 MV proton energy.

Significant upgrades to Birmingham's Dynamitron accelerator are planned prior to commencing a clinical trial. These upgrades will result in an increase in maximum achievable beam current to at least 3mA. At these power levels the current cooling system would be unable to prevent the target melting; further development of the cooling system is therefore required.

Tests of a phase change coolant known as "binary ice" have been carried out using an induction heater to provide comparable power densities to the Dynamitron beam. Binary ice consists of a pump-able slurry of very fine ice crystals suspended in a mixture of water and a freezing point suppressant. This has seen widespread use in direct cooling of food products and in air conditioning heat exchangers. The experimental data shows no improvement over chilled water in the submerged jet system, with both systems exhibiting the same heat input to target temperature relation for a given flow rate.

Current target cooling work is focussed on a novel submerged jet arrangement. CFD simulations and experimental heat transfer data for the new system will be presented.

A critical aspect of high energy lithium target systems is the choice of lithium backing and the methodology used for bonding lithium onto the backing. Birmingham's system uses a copper backing because of its excellent thermal properties. A series of empirical measurements has been used to develop a stable bonding technique. Measurements are on-going to prove that this method

is stable even in conditions where the lithium surface is molten for extended periods of time.

Pa P3 04

Design of Neutron Production Target and Beam Shaping Assembly for 3.5MeV RFQ Accelerator-based BNCT

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The 3.5MeV RFQ accelerator-based Boron Neutron Capture Therapy (BNCT) has been proposed at China Spallation Neutron Source (CSNS). 3.5MeV proton energy is chosen according to the existing RFQ accelerator, and solid lithium target for neutron production via the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction is chosen to supply higher neutron flux for lower accelerator current comparing to beryllium target. The lithium target is intended to accept 30kW proton beam power and present thermal and radiation blistering challenges.

Thermal removal design of the lithium target is carried out with the aid of the CFD packages CFX. Li/Pd/Cu three layer target is proposed for the purpose of avoiding the radiation blistering and is modeled in CFD simulation. The concept of microchannel cooling target and conic target using water as coolant are examined. The effects of coolant velocity, microchannel parameters and proton beam profile on temperature distribution of target are determined.

Several optimizations were performed to determine the size and materials of Beam Shaping Assembly (BSA) by simulations using the Monte Carlo radiation transport code MCNPX 2.5.0. The BSA consists in a cylinder of moderator materials surrounded by reflector and with gamma shielding and thermal neutron delimiter. FluentaTM, Teflon and AlF₃ as moderator materials are analyzed. The neutron spectra at the exit of BSA and the dosage in terms of RBE Gy as a function of depth in the simplified head phantom placed at the exit of BSA are presented.

Pa P3 05

The Collimator Design of Accelerator-based Epithermal Neutron Beam for Boron Neutron Capture Therapy

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Accelerator-based BNCT has become more and more attractive due to its being able to be installed in the hospital. This study is focused on the collimator design

for a chosen beam shaping assembly (BSA) for 30 MeV/1mA proton bombarded on beryllium target. The chosen BSA composed of iron and FLUENTAL as fast neutron moderator, and bismuth for gamma ray attenuation.

The original collimator design is 70 cm in diameter of base and 25 cm in length, with 14 cm-diameter aperture. The 1st 20 cm is a hollow bismuth truncated cone surrounded by mixture of polyethylene and nature lithium carbonate. The next 5 cm is mainly lead for gamma ray shielding and mixture of polyethylene and enriched lithium carbonate near the beam exit for reduction of the thermal neutron flux. The free-in-air beam intensity of epithermal neutron flux is $\sim 1.7 \times 10^9$ n/cm² sec, with fast neutron and gamma ray dose component $< 2 \times 10^{-11}$ cGy cm²/n. The thermal flux to epithermal flux ratio is ~ 0.05 . For in-phantom calculation, assuming blood boron concentration is 10 ppm and T/N ratio is 3, the advantage depth (AD) is 8.2 cm, advantage ratio (AR) is 3.65, and the maximum therapeutic ratio (TR) is 3.92

Although increasing the length of collimator to 40cm will lower the epithermal neutron flux at the beam exit by 25%, it will improve the fast neutron flux profile at the beam exit. Therefore, the background dose patient receives during the treatment is lower. The AD, AR and the maximum TR remain the same. The treatment time will be within 30 minutes for both cases under 10 Gy (W) limitations for the normal tissue.

If the phantom is 10 cm away from the collimator exit, the AD, AR and maximum TR decrease slightly. The treatment time will increase to ~ 40 minutes. If the blood boron concentration is 25 ppm and T/N is 3, the AD is 9 cm, AR is 5.3, and maximum TR is 5.6. The treatment time can be reduced to within 30 minutes.

Pa P3 06

Experimental study of the 13.5 keV resonance of the $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ reaction at CERN n_TOF facility for BNCT.

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We present the first experimental result of the 13.5 keV resonance of the $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ reaction measured at the neutron time-of-flight facility (n_TOF) at CERN. One of the interests of this measurement is the potential application of ^{33}S as a neutron capturer for Neutron Capture Therapy (NCT). The most important reasons for this study are: the high value of the 13.5 keV resonance of the $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ reaction cross-section, above 20 barn; the 3.1 MeV energy of the emitted alpha-particle, very suitable for cell damage; its range in tissue, about 15 μm ; the good biochemical properties of sulphur (high selectivity tumour/normal tissue ratio of some sulphur compounds); no gamma emission in the $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ reaction; stability of the product ^{30}Si and the existence of sulphur commercial nanoparticles of sizes appropriate for tumour targeting. The dose delivers to tumours by the potential presence of ^{33}S crucially depends on the value of the resonance parameters. The $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ cross-section data are scarce,

only one high energy resolution dedicated measurement can be found in the literature. In addition to this, $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ resonance parameters are discrepant in a factor of two when the sole transmission measurement is compared to the (n,α) measurement [1]. We have shown in previous works that even when the most conservative values of the resonance parameters are used, those of the (n,α) measurement, an important enhancement of the dose in tissue due to presence of ^{33}S is found [2].

For all these reasons and with the goal to provide more accurate data, we performed an experiment for measuring the $^{33}\text{S}(n,\alpha)^{30}\text{Si}$ cross-section at the n_TOF facility at CERN [3]. The n_TOF facility is the neutron facility at CERN dedicated to high energy resolution $(n,)$ and (n,f) cross-section measurements for nuclear technology applications. It is based on the PS accelerator of CERN that delivers 20 GeV proton beam onto a Pb spallation target. Along the 185 m flight path, the beam is cleaned from charged particles. The most important features of the n_TOF neutron beam are the very high instantaneous neutron flux, excellent TOF resolution, low intrinsic background and coverage of a wide range of neutron energies. The setup was based on a fast ionization chamber housing ten Micromegas detectors that recovered signals from the six ^{33}S samples, two blank samples for background studies and two B_4C samples used as reference. It will be shown the result of the data analysis of the resonance at 13.5 keV, the most important one for neutron capture therapy. The set of resonance parameters obtained will be compared to previous ones by means of simulations of the dose delivered to tumour tissue in NCT. In addition to this, we will briefly discuss other measurements that are planned at n_TOF-CERN facility with application to BNCT [4]. We would like to emphasize the importance to carry out measurements at CERN trying to improve the dosimetry in BNCT.

[1] G.P. Coddens et al, *Nucl. Phys. A* 469,480–496 (1986).

[2] I. Porras, *Phys. Med. Biol.* 57, L1–L9 (2008).

[3] J. Praena et al., *CERN-INTC-2012-006/INTC-P-322* (2012).

[4] J. Praena et al., *CERN-INTC-2014-007; INTC-I-156* (2014).

Pa P4 01

Design and construction of BNCT irradiation facility at Tehran research reactor

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The first attempt to design an appropriate neutron beam at Tehran Research Reactor (TRR) for BNCT was conducted in 1994. The results showed that the neutron flux at none of the beam exits was sufficient for BNCT. Since then, no attempt has been made to design a proper neutron beam at TRR. In the present work, the thermal column of TRR has been modified to provide suitable neutron beam for BNCT. The thermal column is filled by graphite blocks. Thermal and epithermal modes have been designed to meet BNCT neutron beam criteria recommended by International Atomic Energy Agency using Monte Carlo simulation. For the epithermal mode it has been considered that all graphite blocks can be removed from the thermal column. The suggested BSA for epithermal mode, in cylindrical geometry consists of 20 cm Al as a moderator, 35

cm Pb as a reflector, two 5 cm Bi slabs as gamma shield, and two 2mm Cd sheets as thermal neutron filters. The results show that epithermal neutron flux at the exit of the BSA can be 0.65×10^9 n/cm².s. In-phantom dose analysis indicates that the designed neutron beam can be used for treatment of deep-seated brain tumors in acceptable time. In the construction process, it has been found that it is impossible to remove all graphite blocks from the thermal column. This is due to the high gamma dose caused by activated materials in the reactor structure. In the thermal mode, the arrangement of graphite blocks has been modified to provide a thermal neutron beam. The main modifications consist of rearranging graphite blocks and reducing the gamma dose rate at the beam exit. Activation foils and TLD700 dosimeter have been used to measure in-air characteristics of the neutron beam. According to the measurements, a thermal flux is $5.6e8$ (n cm⁻² s⁻¹), a cadmium ratio is 186 for gold foils and a gamma dose rate is approximately 0.57 Gyh⁻¹. The constructed thermal beam has two major advantages: 1) We impose minimal changes in the thermal column structure and these changes do not disrupt the TRR research activities; 2) A sample or phantom can be irradiated outside of the thermal column so we can irradiate desired region of the sample or phantom. Such a designed beam can be used to treat shallow tumors such as skin melanoma

Pa P4 02

Epithermal neutron source at MARIA reactor

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BNCT research program started in Poland in 2001, in former Institute of Atomic Energy in Świerk (now the Institute is included to National Centre for Nuclear Research). The underwater neutron line for BNCT was mounted along the H2 horizontal beam tube of the research reactor MARIA in Świerk. At that time the line consisted of two pneumatic caissons coupled with a pneumatic system for emptying/refilling. The neutron spectrum of the beam contained mostly thermal neutrons, so a fission converter was designed at the mouth of the channel, but never constructed. After six years in the reactor pool, one of the caissons was broken. It was decided to remove both caissons and to replace them by one pipe coupled with the same pneumatic system as before. A new concept of an underwater, in pool fission converter has been elaborated and the line was constructed in 2010.

According to the new concept, the uranium converter is located in the reactor pool, near the front of the H2 channel. Tubular design of the internal channel makes the construction resistant to mechanical load. The converter consists of 99 densely packed fuel elements EK-10 with enrichment of 10 %, placed in the triangle lattice with the distance of 12 mm. All fuel elements were carefully re-attested with special attention to leak tightness. There is a possibility to remove the converter and to replace it with an aluminium dummy. It is also possible to mount the converter after turn by 180° around the vertical axis, in order to equalize thermal and neutron loads. A measuring probe with two thermocouples

measures the temperature increase in the converter. The line was equipped with moderator-filter system made with lithium fluoride; nickel, titanium, bismuth and B₄C.

Monte-Carlo calculations showed that the total neutron flux density at the entrance to the converter is of about 10^{13} n cm⁻²s⁻¹ and flux density of epithermal neutrons at the entrance to the filter/moderator of the beam is of about $2 \cdot 10^9$ n cm⁻²s⁻¹.

At present, the line is technically ready for use. In 2013 the scientific NCBJ program "Neutrons H2" was set in cooperation with AGH University of Science and Technology, Oncology Centre and Warsaw University of Technology. In March 2014 National Centre for Nuclear Research decided finally to put converter into reactor MARIA. The program "Neutrons H2" includes building research-training stand for BNCT.

Pa P4 03

Mock-up Experiment at Birmingham University for BNCT Project of Osaka University - Outline of the Experiment

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Osaka University is now starting development of a new accelerator-based neutron source (ABNS) for BNCT under the collaboration with Sumitomo Corporation and Mitsubishi Heavy Industries Mechatronics Systems, Ltd. The ABNS employs an electrostatic accelerator which produces low energy neutrons of $\sim 10^{13}$ n/sec having several hundreds keV via p-Li (⁷Li(p,n)⁷Be) reaction. By this neutron source, exposure dose of patients could be suppressed substantially. In the present paper, outline of mock-up experiments is described which was carried out at Birmingham University, UK, with a moderator/collimator assembly newly designed and constructed by the authors' group.

In 2011, after critical discussion on the basic design principle of our ABNS, two demonstration experiments were carried out. In 2012, source term measurement for p-Li reaction was conducted at the dynamitron accelerator facility in Tohoku University. A mock-up of moderator/collimator assembly of the ABNS was thereafter designed and constructed based on the result of the Tohoku University experiment. From 2013 May to June the mock-up experiments with the assembly were performed at Birmingham University with a human body phantom to characterize the neutron irradiation field.

In the experiment, the proton beam current and energy were several hundreds μ A and 2.1~2.8 MeV, respectively, to demonstrate our new ABNS. As collimator/

moderator material, boric water and lead were used for neutron and gamma-ray shield, respectively. Neutrons were moderated with a pair of material having different moderation performance made of light and medium heavy material. Just under the assembly an enough space was kept for setting the human body phantom, in which spatial distributions of neutron flux intensity and gamma-ray doses were measured with gold foils and glass dosimeters, respectively. Now we are analyzing obtained results. Some of the experimental results will be presented in other two presentations in the Conference. Roughly speaking, the results show a very good agreement between experimental results and calculations as predicted in the design so as to show that our design tools are quite reliable for designing our new ABNS.

Completing the data analysis of the experiments, we are starting design of the new accelerator, lithium loop, moderator/collimator assembly and so on under the collaboration with Sumitomo Corporation and Mitsubishi Heavy Industries Mechatronics Systems, Ltd.

Pa P4 04

Construction of a convenient head phantom for BNCT experiments of Tehran research reactor

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The potential of the thermal column of Tehran research reactor (TRR) to provide a neutron source for BNCT has been investigated recently. This is the first time that BNCT experimental studies are performed in thermal column of TRR. For validation of the planning and the establishment of a procedure for treatment plan and dose reporting, it is necessary to determine the absorbed dose and separate the various contributions due to each different secondary radiation. These dose components are estimated by in phantom experiments. The main objective of this study is to design a convenient head phantom for BNCT dosimetry measurements of TRR. Shape of the phantom is based on the Snyder head model. It is an ellipsoidal acrylic walled anthropomorphic dosimetry phantom. In order to insertion of dosimetry devices in the phantom volume, the phantom base is provided with 31 ports. One port on the phantom center line and others on two concentric circles. Point dose measurement devices such as activation foils, wires, TLDs and small ion chambers can be placed in many locations within of the phantom. The designed phantom can also be filled with gel dosimeter. It can be concluded that designed phantom is suitable for BNCT dosimetry measurements. It is close to human head and the design permits the measure of all relevant dose components at many locations within the phantom. Also the three- dimensional dose maps can be obtained. These dose maps permits to provide data for comparison with computational treatment planning codes and beam development. This design is under construction and is the first BNCT phantom in Iran.

Pa P4 05

Study of suitability of Fricke-gel-layer dosimeters for in-air measurements to characterise epithermal/thermal neutron beams for NCT

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Dosimetry methods based on laboratory-made Fricke-Xylenol-Orange gels have shown remarkable potentiality for in-phantom or in-air dose measurements, with separation of the different dose contributions. The separation of dose components is achieved by the analytical comparison of the doses obtained with a standard gel dosimeter, a dosimeter similar to the standard one but added with proper amount of ¹⁰B and a dosimeter with the same composition of the standard gel but prepared with heavy water instead of water. For in-phantom measurements, suitable dosimeter shape and size was utilised, depending on phantom dimension. In any case, the variation of the isotopic composition of the dosimeters does not affect neutron transport, because this is determined by the composition of the phantom surrounding the dosimeter.

For measurements of free-beam characteristics, the dosimeters were always prepared as layers 3 mm thick, with diameter from 10 to 14 cm, so to cover the mouth of the beam collimator. The total thickness of the dosimeters (Fricke gel plus polystyrene sheets) is of 5 mm. In such measurements without phantom, it is appropriate to evaluate whether and how much the material of which the dosimeter is composed modifies the characteristics of the beam. To this aim, measurements and calculations have been executed.

Irradiations were carried out at the BNCT epithermal neutron column of the LVR-15 research reactor, in Rez. Two beam configurations have been inspected: i) measurements with the BNCT epithermal beam, at the exit of the epithermal neutron column; ii) measurements in the same position of the epithermal column, but with a neutron beam moderated by a disk of polyethylene, 2 cm thick, inserted into the collimator mouth.

Control measurements have been performed by means of thermoluminescence detectors of LiF:Mg,Ti, mainly TLD-700 chips (Harshaw). The TLDs were exposed in two configurations. One group was held between two strips of polystyrene (1 x 20 x 160 mm³) and placed against the mouth of the collimator, along a diameter. Other TLDs were inserted in the gel of a fake circular dosimeter large as the mouth of the collimator, to obtain a map of the gamma dose and of the thermal neutron fluence in the volume of the gel dosimeter sensitive material. Gamma dose and thermal neutron fluence have been obtained from the TLD glow curves (GCs), with a method recently proposed, based on the shape of the GCs. The values of gamma dose and thermal neutron fluence obtained in the two configurations were compared with the results obtained with gel dosimeters.

Monte Carlo simulation, with MCNPX code, have been developed for inter-comparison with experimental results.

Pa P4 06

The improvement of the energy resolution in epi-thermal region of Bonner sphere using boric acid solution moderator

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Introduction

In epi-thermal neutron irradiation field for BNCT, neutron energy is over a wide range. Because neutron effect to tissue greatly vary depending on its energy, it is necessary to evaluate the neutron dose for each neutron energy. Thereby, it is important to obtain the detailed information for the neutron energy spectrum before the clinical use.

Bonner sphere is useful to evaluate the neutron spectrum in detail. We are improving the energy resolution in epi-thermal region of Bonner sphere, using the boric acid solution (¹⁰B 0.14wt%) as a moderator. Its response function peak is narrower than that for polyethylene moderator and the improvement of the resolution is expected. The resolutions between polyethylene moderator and boric acid solution moderator were compared. The neutron spectrum was measured for the epi-thermal neutron irradiation mode at Heavy Water Neutron Irradiation Facility of Kyoto University Reactor (KUR-HWNIF) using these Bonner spheres.

Materials and Methods

In this study, Bonner sphere consists of a spherical neutron moderator shell and activation foils placed in the sphere center as thermal neutron detector. Manganin and gold are used as activation foil material. The specific saturated activities per flux for each energy neutron were calculated as the response function of Bonner spheres. Calculations were performed using a Monte Carlo simulation code system, PHITS. The sphere diameters were 10, 15, 20 cm.

In the comparison of energy resolution, their response functions were calculated for homogeneous parallel beam. Calculation was performed using synthetic neutron spectra consisting of a single peak in epi-thermal energy region. The calculated activities were unfolded into estimated spectrum by UMG unfolding package using uniform spectrum as the default. The energy resolution comparison was made judging from the peak shapes of the estimated spectra.

In the activity measurements and spectrum evaluation, water and boric acid solution were used as moderators. Their response functions were calculated based on beam data of previous study and the practical geometry. Neutron irradiations were performed on the epi-thermal neutron irradiation mode at KUR-HWNIF. A HPGe detector was used for the activity measurements. The neutron spectrum was obtained from the activity data by UMG.

Results

From the comparison for the shape of the estimated spectra, it was confirmed

that boric acid solution moderator improves the energy resolution of the Bonner sphere.

The estimated spectrum was in good agreement with the data from the previous study. The estimated spectrum in epi-thermal region changed by twenty and a several percentage if the foil position varied by 5mm or the boric acid concentration did by ^{10}B 0.03wt %.

Conclusion

The improvement of the energy resolution of Bonner sphere using boric acid solution moderator was confirmed. In the future work, we will make a more detailed evaluation of the energy resolution with pseudo-inverse matrix and averaging kernel method. And, we will perform optimization study to achieve high energy resolution.

Pa BI2 01

Autoradiographic and histopathological studies of boric acid-mediated BNCT in hepatic VX2 tumor-bearing rabbits: specific boron retention and damage in tumor and tumor vessels

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Introduction

Hepatoma is a malignant tumor that responds poorly to conventional therapies. Boron neutron capture therapy that can provide a better way of delivering curative dose to tumors while sparing normal liver tissue has the advantage for hepatoma therapy. Our study showed liver tumor can be successfully cured by boric acid (BA)-mediated BNCT and the blood flow within and around the tumor changed from rich blood supply to poor blood supply after BNCT in rats and rabbits model.

Materials and Methods

A multifocal hepatic VX2 tumor-bearing rabbit model was used to study the mechanisms of BA-mediated BNCT. ^{10}B -enriched BA (99 % ^{10}B) was used as the boron drug. BA powder dissolved in a normal saline solution was administered (50 mg ^{10}B /kg bw) from a marginal ear vein via a bolus injection. The rabbit was sacrificed 35 minutes following the BA injection, and the tumors were removed and frozen. The microdistribution of boron in the 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 for autoradiography. LR115 films (Kodak-Pathe, Paris, France) were directly covered on the slide with a tumor section to undergo neutron capture autoradiography. The slides were placed in a polyethylene (PE) phantom and irradiated with neutrons for 10 min at Tsing Hua Open Pool Reactor. The etched LR115 films were observed under an optical microscope

that was equipped with a digital camera to capture images of the α -tracks. The rabbits that had been intravenously injected with BA (50 mg $^{10}\text{B}/\text{kg BW}$) were irradiated with neutrons 35 minutes following the BA injection. The physical dose, calculated using MCNP (Monte Carlo N-particle) code, was 14 Gy at the tumor-bearing liver. Rabbits were sacrificed on the 5th day following BNCT and a histopathological examination was performed to elucidate the radiobiological effects.

Results

Autoradiography revealed that BA was retained in the tumor and the tumor vessels. A low-density of alpha tracks was observed in normal liver tissue, whereas regional differences in track density were observed within the tumor region: tracks in the central necrotic area had a lower density than those in the active regions of the tumor. The ratio of the number of tracks in the tumor to that in the normal liver tissue (T/N track ratio) reached 2.5, and the ratio of the number of tracks in the vessels to that in normal liver tissue (V/N track ratio) reached 2.3. Accordingly, BA-mediated BNCT targeted more boron dose to tumor cells and tumor blood vessels than to normal liver tissue. Histopathological observations of a VX2 tumor-bearing liver of the rabbit five days after BNCT revealed no obvious damage to the hepatocytes or vessels in the normal liver regions, whereas, tumor cells were damaged and underwent fibrosis as well as necrosis in vessels of the tumor region. Histopathological changes in the artery in the VX2 tumor were also observed: multiple, moderate arteritis was expressed as endothelial cell degeneration and edema with inflammatory cell infiltration around the peri-tumor area, as determined by comparison with normal arteries.

Conclusion

The microdistribution of α -tracks demonstrates that BA is highly targeted to tumors and tumor vessels, while normal tissues are spared. The killing of tumor cells and the disruption of tumor blood vessels may be responsible for the success of BA-mediated BNCT for liver tumors.

Pa B12 02

Neutron autoradiography in nuclear track detectors: simultaneous observation of cells and nuclear tracks from BNC reaction by UV C sensitization of polycarbonate

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Introduction

The distribution and concentration of ^{10}B atoms in biological samples coming from BNCT protocols can be determined through the analysis of the tracks forming its autoradiography image on a nuclear track detector. We have developed a qualitative but also a quantitative autoradiography analysis and validated our quantification system by ICP-OES and ICP-MS measurements. In order to obtain the autoradiography image, an etching must be performed

and the biological sample (e.g. tissue section or cell cultures) is lost. For certain applications, the location of boron atoms inside the cell could be known more precisely by the simultaneous observation of the nuclear tracks and the sample image on the detector. In this work we present a methodology to produce an "imprint" of cells cultivated on a polycarbonate foil by exposure of the detector to UV C radiation.

Materials and Methods

Cells of a human metastatic line of melanoma (MELJ) were seeded on 250 μm thick polycarbonate foils (Lexan™). They were incubated with BPA (10 μg ^{10}B /mL) for 2 h, washed and fixed and then exposed to thermal neutron fluences of 10^{12} n.cm $^{-2}$ and 10^{13} n.cm $^{-2}$. Three groups of these samples were irradiated with a 15 Watt, 254 nm wave length lamp, for 2, 4 and 6 h. At the irradiation position, the irradiance was 4.65 ± 0.04 mW.cm $^{-2}$. Then, the cells were stained and explored with a light microscope. The foils were processed with a KOH solution at 70° C for three different times: 2, 3 and 4 min. The previously delimited areas were scanned and photographed with an imaging system connected to a plain light microscope. Track density was determined and converted into ppm values through a calibration curve. The morphology of the imprint was analyzed by both light and scanning electron microscopy. Samples exposed to UV A radiation were also analyzed (360 nm, at the same irradiance as UV C lamp).

Results

Under these seeding conditions, an appropriate monolayer cells distribution could be obtained. UV C exposure does not affect cell visualization. The images of both cells and nuclear tracks were found to be optimal for a neutron fluence of 10^{13} n.cm $^{-2}$, UV C exposure during 6 h and an etching time of 4 min. The etch pits are only present inside the cells imprints, indicating a preferential boron uptake. Eventual need of correction factors due to cells' thickness was analyzed with a previously developed stochastic simulation of tracks development and detection. An average value of 40 ± 5 ppm was obtained inside the MELJ cells. From the analysis of the samples exposed to UV A, it could be observed that, despite having undergone irradiance conditions comparable to those used with UV C radiation, there was no cellular imprinting registered on the detector surface. In this way, we confirmed that this phenomenon is dependent on wavelength. From our results it could be concluded that the photoinduced damage mechanisms of the polymeric detector responsible for the imprint creation are more effective for photon energies higher than that corresponding to UV A radiation. Tissue slices were also analyzed with this technique and the preliminary results will be presented.

Conclusions

A simple and accessible method was developed for simultaneous visualization of cells and nuclear tracks. Images of cells and nuclear tracks can be clearly distinguished using light microscopy. Polycarbonate showed to be an advantageous detector material also for this alternative neutron autoradiography technique. This methodology paves the way for an extensive comparison between cell lines response to BNC treatment and for the evaluation of different boron compounds effect, through their distribution in vitro. Application of the proposed technique to these studies is in progress.

Pa BI2 03

Inter-comparison project for boron concentration determination at INFN-University of Pavia (Italy) and CNEA (Argentina)

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Introduction

In order to improve the knowledge about the physiological behavior of ¹⁰B in BNCT protocols, it is necessary to determine not only gross ¹⁰B concentration but also to study its microdistribution in tumor and surrounding tissue. The alpha spectrometry technique (α -spect) is based on charge particle spectroscopy and was fully developed at the University of Pavia. Online global values of boron concentration in thin tissue samples can be obtained with this methodology. Complementary, the quantitative neutron radiography (NCR) based on CR-39 solid state nuclear track detector (SSNTD) has been set up in order to analyze boron microdistribution. In Argentina, at the National Atomic Energy Commission (CNEA), a quantitative neutron autoradiography (QTA) technique using Lexan as nuclear track detector has been developed and validated with ICP-OES and ICP-MS. In view of the extensive collaboration between both groups, an inter-comparison protocol of the boron determination methodologies is required.

Materials and Methods

Different samples were analyzed in order to compare the techniques: (a) aqueous boric acid solution, (b) liver homogenates prepared with different boron concentration values ranging from 0 to 75 ppm and (c) liver sections of rats injected with BPA at different doses. Samples of (a) were quantified with both neutron autoradiography techniques and the irradiations were performed using a specific setup for each methodology. (b) and (c) samples were sectioned with a cryostat and mounted on mylar disks for alpha spectrometry, polyallyldiglicol (CR-39) for NCR and polycarbonate (Lexan) for QTA. The SSNTD foils were irradiated at the TRIGA Mark II reactor (Italy) and the RA-3 reactor (Argentina), respectively. The etching was performed with PEW at 70 °C solution at 10 min (NCR) and 2 min (QTA). Track density was evaluated and converted into boron concentration by previously developed calibration curves. The boron concentration values of the alpha spectrometry were determined from the energy spectrum obtained by the irradiation of the sample sections at the end of the thermal column of the TRIGA reactor.

Results

All samples gave rise to homogeneous autoradiography images, thus gross values were obtained from the three methodologies. With the established conditions, QTA tracks were originated by alpha and lithium particles, whereas only alpha particles were counted for NCR. Aqueous solutions prepared in both laboratories showed equivalent autoradiography images. Differences in boron concentration values of the liver homogenates were found to be not statistically significant. Liver samples are still under evaluation, but the obtained results are consistent with previously reported values.

Conclusions

From these findings, we can conclude that it is possible to compare these three methodologies and obtain equivalent boron concentration values. This inter-

comparison protocol contributes to a better understanding of each technique and paves the way for their application to BNCT protocols that are being carried on in collaboration between both countries.

Pa BI2 04

Improvement of a PGNA Facility for BNCT in THOR

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The dose delivered during Boron Neutron Capture Therapy (BNCT) is highly depended on boron concentration accumulated in tumor region. Accordingly, the information of boron concentration in blood is essential. In order to not only accurately but rapidly measure boron concentration in blood samples, a Prompt Gamma Neutron Activation Analysis (PGNA) facility is being under construction at E2 beam port of Tsing Hua Open-pool Reactor (THOR). THOR is a 2MW swimming pool research reactor with seven horizontal neutron beam tubes, including BNCT epithermal neutron beam, extending straightly from the reactor core. Construction design of E2 beam was performed in previous work and the installation of beam collimation plug was completed subsequently. For the purpose of maximizing thermal neutron flux at the beam exit, a cylindrical concrete beam collimation plug with an aperture of 1 inch was adopted. As a result, however, a tremendous amount of fast neutrons and gammas will come out directly from the core. Therefore, these undesired contaminations result in high background dose rate surrounding the PGNA facility and in addition, cause significant dead-time loss during prompt gamma ray measurement. The objectives of this work are to reduce severe background contaminations as well as to maintain sufficient thermal neutron flux at blood sample position of the PGNA facility. To lower background contaminations, a shielding assembly using lead and borated polyethylene was employed at a distance of ~50 cm, due to the limitation of beam port geometry, away from E2 beam exit. Background gamma dose rates with and without shielding assembly were measured and compared. A preliminary result showed that gamma dose rate surrounding the PGNA facility decreased significantly, with 5 to 25 times lower depending on different measuring position. Nevertheless, gamma dose rate close to E2 beam exit was still too high. Neutron flux measurement utilizing double foil method was also performed. It was found that thermal and epithermal neutron flux at E2 beam exit were, respectively, $\sim 4 \times 10^7$ and $\sim 3 \times 10^7$ neutrons/cm²-sec, when reactor operated at 1.2MW. Note that self-shielding effect was not taken into consideration. Even though the result was encouragingly agreed with expectation of previous design but meanwhile, unfortunately, it remains a challenge to establish a sample holder system at beam exit due to the insufficient space. Therefore, considering different figures of merit, a new beam shielding assembly extending directly from E2 beam exit was taken into account as an alternative and will be designed and manufactured. Performance test on remodeled PGNA facility will be accomplished and demonstrated in the near future.

P

a B12 05

Basic property of array-type CdTe detector for BNCT-SPECT

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Our research group has been developing a device in order to know treatment effect of BNCT (Boron Neutron Capture Therapy) in real time. We named it BNCT-SPECT. In more detail, BNCT-SPECT can obtain a three-dimensional image of the BNCT treatment effect (local radiation exposure dose) by measuring 478keV gamma-rays emitted from the excited state of ⁷Li nucleus created by ¹⁰B(n, α) reaction. On the development, there are severe conditions as shown in the following:

(1) 478keV gamma-rays should be detected with a good spatial resolution of about several mm. (2) Energy resolution, full width at half maximum (FWHM), should be less than 33keV (511keV-478keV) so as to measure annihilation and 478keV gamma-rays separately. (3) Measurement of 478keV gamma-rays should be carried out in a high statistical accuracy. (We aimed at the net count per hour at the photo-peak being more than 1000.) (4) Signal to Noise(S/N) ratio should be more than unity under a background field of a high neutron flux intensity.

At First, we selected a CdTe detector as an elemental measuring device for BNCT-SPECT, because it has high detector efficiency and good energy resolution. Next, we fixed the necessary dimensions of the elemental CdTe detector by theoretical calculations. The size of the CdTe crystal was determined meeting condition (1) above. Then, we confirmed experimentally condition (2), that is, feasibility of separate measurement of 478keV and annihilation (511keV) gamma-rays.

In the present study, we have been investigating an array-type CdTe detector for the BNCT-SPECT system considering the detector assembly, irradiation room and even arrangement of arrayed CdTe crystals. Under these circumstances, condition (3) was confirmed to be met, however, the S/N ratio did not meet condition (4). Also, the most probable cause that the target value was not achieved an influence of Compton scattering especially due to capture gamma-rays of hydrogen. Theoretical calculations were carried out to find out whether anti-Compton measurement in the array-type CdTe detector could work to decrease the noise due to Compton scatterings. The calculation result successfully showed that the anti-coincidence measurement would possibly increase the S/N ratio. We thus produced an arrayed detector with two CdTe crystals. The CdTe detector size is 2×2.5×40mm, which is the maximum dimensions achieved at present in Japan. The basic performance, such as energy resolution and detection efficiency, were measured. Also, we examined whether the influence of Compton scattering could really be reduced with the developed CdTe detectors using the anti-coincidence technique.

From the experimental results, we confirmed the basic performance was as predicted and verified the feasibility of anti-coincidence measurement to improve the S/N ratio. From the obtained basic property of the array-type CdTe detector with two crystals we will design and develop a proto type real arrayed detector for BNCT-SPECT.

Pa BI2 06

Detecting BNCT prompt gamma and neutron spectra with a CdTe detectorsA. Winkler¹, H. Koivunoro², V. Reijonen², I. Auterinen³, S. Savolainen², R. Orava¹¹*Department of Physics, University of Helsinki, POB 64 FI-00014 Helsinki, Finland,*²*HUS Helsinki Medical Imaging Center, HUCH, POB 340, FI-00029 HUS, Finland,* ³*VTT Technical Research Centre of Finland, Espoo, POB 1000, FI-02044 VTT Finland*
email: alexander.winkler@helsinki.fi**Introduction**

The boron neutron capture reaction results in emission of prompt gamma radiation at 478 keV, which can be measured during the treatment to determine the absorbed dose delivered to the patient in boron neutron capture therapy (BNCT). In this work, we study the performance of a novel high-resolution CdTe gamma spectrometer for this purpose. We also study the ability of the same detector to measure neutron spectra.

Materials and Methods

We used two CdTe based spectrometers: a 10-y-old custom built device and a current commercial product. The measurements were carried out using an epithermal neutron beam produced at TRIGA Mark II type FiR1 research reactor in Espoo, Finland. A cylindrical PMMA phantom with 2 small boronated plastic pallets (3-w% B¹⁰) set inside was placed in the beam line, while the detectors were placed perpendicular to it, at distances of 18 cm and 14 cm, respectively, from the beam center. Additionally a 3 mm Pb shield, in front of the detectors, was used to protect the electronics from the radiation. Spectra were acquired for the setups of free beam (no phantom), pure PMMA phantom (no pallets) and the PMMA phantom with the pallets, up to a maximum reactor power of 2.5 kW. Additionally the photon and neutron spectra at the detector locations were simulated with MCNP5 radiation transport model to compare with the experimental data.

Results

All measured spectra are exceptionally high in resolution and sensitivity for the prompt gamma photons of the cadmium neutron capture reactions. The peaks are clearly visible at the prominent locations and were measured with an excellent energy resolution of 0.5 % and 1 % for 558.6 keV and 651.3 keV, respectively. The 478 keV prompt gamma peak originating from the boron neutron capture reaction could be seen in the PMMA setup with the pallets. The comparison to the simulation spectra shows similar behavior for both spectra at the points of interest (478 keV, 558 keV). However, the strong 511 keV annihilation peak present in the simulations could not be found in the measured spectra.

Conclusion

A decade ago background suppression and spectral resolution proved difficult in using CdTe (and the similar CdZnTe) detectors for BNCT treatment set-ups. According to our measurements, improvements in CdTe detector technology in terms of energy resolution have made the detector type feasible for observing and quantifying the 487 keV gamma peak as well as other prompt gammas in the photon spectrum. The new detector type has proven to be developed enough to provide the energy resolution needed in BNCT. Additionally these detectors can measure the prompt gamma photons resulting from the cadmium neutron

capture reaction, allowing the detector to simultaneously measure and separate signals from both boron neutron and cadmium neutron capture reactions, hence acting as a gamma and neutron detector at the same time.

Wednesday June 18th

PI B2 01

Boron Neutron Capture Therapy (BNCT) Mediated by Boronated Liposomes for Oral Cancer in the Hamster Cheek Pouch Model

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Given that more effective, less toxic, and minimally invasive therapies are needed for head and neck cancers, we previously proposed and validated the use of the hamster cheek pouch model of oral cancer to explore new applications and study the radiobiology of BNCT. Oral mucositis limits the radiation dose that can be administered. In addition, the inflammatory process associated with moderate mucositis in field-cancerized tissue could favor tumor development from this tissue. Within this context, BNCT protocols that minimize mucositis are more likely to deliver therapeutically useful radiation doses to the tumor without exceeding normal and precancerous tissue tolerances.

Current progress of our study, which seeks to maximize the therapeutic efficacy of BNCT for treatments of head and neck cancers, while minimizing mucositis in precancerous tissue will be presented. The aim of the study was to assess tumor response and potential toxicity of BNCT in the hamster cheek pouch oral cancer model, employing a liposomal boron carrier.

We assayed Single and Double application protocols of BNCT mediated by the liposomal boron carrier with an interval of 4, 6 or 8 weeks between applications. Due to good therapeutic outcome, it was possible to extend follow-up from the previously established 4 weeks to 16 weeks. The Double application protocols sustained the Single application tumor response over the longer experimental period. No normal tissue radiotoxicity was observed. A salient advantage of the liposomal boron carrier was that only mild mucositis in dose-limiting precancerous tissue was associated to a sustained tumor response of over 70 %.

PI B2 02

Preliminary study of Sequential BNCT in an oral precancer model: a novel BNCT approach to treat tumors and inhibit the development of second primary tumors from surrounding precancerous tissue

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Introduction

The clinical relevance of the search for new therapeutic strategies for head and neck squamous cell carcinoma lies in the relatively poor 5-year survival rate and the large tissue defect caused by radical surgery. We previously evidenced the therapeutic efficacy of BNCT to treat oral cancer in the hamster cheek pouch model. Although dose escalation would conceivably serve to optimize therapeutic outcome, it is limited by mucositis in the dose-limiting precancerous tissue. We previously demonstrated that Sequential-24h-BNCT (BPA-BNCT followed by GB-10-BNCT 24 h later), a novel approach to BNCT, allows for higher doses to be delivered to tumor, enhancing tumor response at no extra cost in terms of toxicity in the dose limiting precancerous tissue, at short term follow up. Based on these results, the aim of the present work was to study mucositis and therapeutic efficacy of Sequential-24h-BNCT in our model of oral precancer, at longer follow up times. The clinical relevance of studying precancerous tissue at longer follow up times is the frequent occurrence of second primary tumors and mucositis after treatment, a very common side effect in BNCT and conventional therapies. Thus, in a clinical scenario, controlling tumor response while inhibiting tumor development in surrounding precancerous tissue, without significant radiotoxic effects, would be a very useful approach.

Materials and methods

The DMBA-cancerized pouch of 2 groups of hamsters was exposed to: 1) Seq-24h-BNCT at 9 Gy mean total absorbed dose (n=3); 2) Seq-24h-BO: Sequential Beam only (n=5). These groups were compared to previously studied protocols for the treatment of precancerous tissue: *Single* BPA-BNCT and *Single* (GB-10+BPA)-BNCT, 8 Gy mean absorbed dose and *Double* BPA-BNCT and *Double* (GB-10+BPA)-BNCT, 4 weeks apart, 10 Gy mean total absorbed dose. All animals were irradiated at RA-3. Cancerized, sham-irradiated hamsters (n= 88) served as a control group to follow tumor development from precancerous tissue in untreated animals. Animals were followed for 3 months.

Results and Conclusion

SBNCT (8 Gy) exhibited severe mucositis in all animals. Instead, DBPA-BNCT and D(GB-10+BPA)-BNCT, 4 weeks apart, 10 Gy mean total dose and Seq-24h-BNCT exhibited a reduction in severe mucositis (66 %, 33 %, 66 % respectively). As to tumor development, D(GB-10+BPA)-BNCT and Seq-24h-BNCT showed lower percentages of animals with new tumors after treatment (33 % in both cases) versus beam only (83 and 80 % respectively) and control group (79 %). This preliminary study would suggest the potential use of Seq-24h-BNCT to treat precancerous tissue. Both protocols, D(GB-10+BPA)-BNCT and Seq-24hs-BNCT were shown to be useful to treat tumors and precancerous tissue at a lower cost in terms of toxicity. Double BNCT (4 weeks interval) could conceivably reduce large tumors to improve dose distribution for the second application whereas Seq-BNCT could deliver a high, therapeutically effective dose to smaller tumors with only a one day interval at no cost in terms of toxicity.

PI B2 03

First results of pre-clinical studies of BNCT for Osteosarcoma

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Introduction

BNCT application is being investigated for limb osteosarcoma (OS) in Pavia, Italy. This tumour is characterized by an infiltrative nature that makes difficult its surgical removal without positive margins. OS is a radio-resistant tumour with a high probability of local recurrence or lung metastases and it usually affects a young population. BNCT could be an option as adjuvant therapy thanks to its selectivity in targeting tumour cells infiltrated in normal tissue and to the biological effectiveness of the high LET radiation. Pre-clinical studies are meant to verify ¹⁰B selective uptake in a rat model of OS treated with BPA. The effectiveness of BNCT for OS is assessed by animal irradiation in the thermal column of the TRIGA reactor of Pavia University. Finally, treatment planning simulations have been performed in order to establish the optimal characteristics of the neutron beam to be employed for patients.

Materials and Methods

Sprague-Dawley rats were inoculated with UMR-106 cells to generate limb OS as described in [Ferrari et al., ARI, **67**, 2009, S341–S344]. Two BPA administration routes were employed: intra-peritoneal and local intra-muscular injection. The animals were sacrificed 4 hours after administration and healthy muscle and OS were taken for boron measurements by neutron autoradiography and alpha spectrometry. As the methods to analyze hard tissues such as bone is still under development (see Provenzano et al., this congress), the muscle surrounding the tumour was taken as the reference value for the healthy tissues. OS developed in animals could be sectioned as a soft tissue.

Animals treated with BPA were irradiated in the thermal column of the TRIGA reactor, inside a neutron shield that exposed only the limb, in a position where the thermal neutron flux in air is $1.2 \cdot 10^{10}$ n/cm² s. Healthy animals and animals with OS were irradiated 4 hours after BPA administration, testing both local and intra-peritoneal administration. A group of animals were irradiated without BPA and another group served as control for tumour growth evaluation.

CT scan of a patient affected by limb OS was employed for treatment planning simulations by NCTPlan and MCNP5. Different ideal beams were tested from the point of view of dose distributions, with energy ranging from thermal to epithermal in a one-beam configuration. Realistic neutron spectra from nuclear reactor and accelerators were also tested in order to determine the most suitable

realistic beam to treat OS. Boron concentration in muscle and in OS was set as measured in rats and other tissues were assumed to uptake typical boron concentration.

Results

Boron concentration measurements show high variability between animals even within the same protocol. On average, intra-peritoneal BPA administration shows a higher uptake both in healthy muscle (between 15 and 20 ppm) and in tumour (between 30 and 60 ppm) in comparison to the other protocol, and the ratio of boron concentration ranges from 2 to 4. Local administration shows poorer selectivity, the healthy muscle and the tumour taking-up around 10 ppm.

The shield was proven to be suitable for irradiation in the thermal column of the TRIGA reactor, allowing to protect the body and to preserve the animals from adverse irradiation effects. Tumour growth evaluation and normal tissues effects are under evaluation and will be presented.

The treatment plan simulations employing the CT scan of patient show that it is possible to obtain a favorable dose distribution in tumour without exceeding the tolerance limits for skin and for the other tissues involved in the irradiation.

PI P1 01

Verification of Tsukuba Plan, a new treatment planning system for BNCT

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Introduction

At present, some accelerator based BNCT facilities are developed in Japan. In Kyoto University, clinical trials using a cyclotron based neutron source (C-BENS) are being performed. The C-BENS system is also being installed to Southern Tohoku Hospital in Fukushima Prefecture. And University of Tsukuba and National Cancer Center Hospital are developing a linac based BNCT device, respectively. To conduct BNCT using the accelerator based neutron sources, University of Tsukuba is developing a new treatment planning system (tentative name: Tsukuba Plan).

For dose calculation engine, Tsukuba plan has employed PHITS and JENDL.PHITS is a multi-particle Monte-Carlo transport code, and JENDL is a nuclear cross-section data developed in Japan. And to precise dose calculation effectively, the system has applied voxel calculation method which had a good record with BNCT dose planning. To apply the system to actual treatment planning of BNCT, we are conducting several verifications.

Materials and Methods

First, applicability of JENDL to dose calculation for BNCT was confirmed by comparison with ENDF/B calculations. ENDF/B has already applied to NCTplan and JCDS as treatment planning systems for BNCT. A simple phantom model was constructed and distributions for neutrons and several dose components in the phantom were calculated by combination with JENDL or ENDF/B respectively. The characteristic of JENDL was confirmed by comparison with ENDF/B calculations.

Next, to verify accuracy of dose estimation and calculation speed for the voxel calculation model, several voxel models for a simple rectangle shape phantom are created using Tsukuba plan. In the verification, the voxel cell size formed of the model were changed from 5mm³ (1x1x5mm³) minute voxel cells to 80mm³ (4x4x5mm³) large voxel cells. And tally size were also changed in accordance with the voxel size. The Monte-Carlo transport calculations for each model were computed using 80 CPU parallel computer, calculation time (speed) for each model were estimated. The calculation results and their times for each voxel model were compared.

To validate applicability of Tsukuba Plan to actual treatment planning work, human model was created using patient CT images and then distributions of neutrons and several doses were determined. The three-dimensional distributions of each doses and dose volume histograms (DVH) for each ROI were determined. The dose distributions and DVHs in same condition were estimated by JCDS, and finally the results of Tsukuba Plan were compared with the JCDS calculations.

Results and discussions

The values of total equivalent dose determined by JENDL calculation were in good agreement with ENDF/B calculations. Thus the results demonstrated that JENDL can apply to dose calculation of Tsukuba Plan. And calculation results of Tsukuba Plan for the real human model were also comparable with JCDS calculations. These verification results proved that Tsukuba Plan can perform treatment planning for BNCT in practical use.

In the future, Tsukuba Plan is installed to Kyoto University and we will carry out actual treatment planning work for BNCT performed in KUR. The results are compared with SERA estimations. And Tsukuba Plan will be also applied to clinical trials in University of Tsukuba and Southern Tohoku Hospital.

PI P1 02

BNCT Treatment Planning for Superficial and Deep-Seated Tumors : Experience from Clinical Trial of Recurrent Head and Neck Cancer at THOR

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Clinical trial of recurrent head-and-neck cancer for Boron Neutron Capture Therapy (BNCT) at THOR started on August 11, 2010 under the collaboration between National Tsing Hua University and Taipei Veterans General Hospital. Up to January of 2014, 17 patients were treated. This study shows the selection of treatment setup based on experience on patients with superficial and deep-seated tumors. In-house designed treatment planning system THORplan was used. Normally, the prescribed radio-biologically dose is to give at least 20 Gy (W) to 80% of GTV. The location in GTV targeted to receive this dose is called D80.

Tumor of patient 17 was large and superficial. A patient collimator of 16-cm-long with exit diameter of 10 cm was used. Comparing to the direct radiation, the use of patient collimator resulted in higher thermal neutron flux at the tumor location. The dose rate at tumor D80 location was 16 % higher and the irradiation time could be shortened by

14 %. Although the use of collimator also increased the maximum dose rate of mucosa by 2 %, due to the shorter irradiation time, the maximum total dose of mucosa decreased by 12 %. In addition, the use of collimator resulted in decrease of fluxes outside the irradiation field, and would provide better protection for the normal tissues outside the irradiation field.

Tumor of patient 16 was small and deep-seated. The use of patient collimator (10-cm-long with exit diameter of 10 cm) in this case showed no benefits since the tumor did not located inside the 2-cm region where thermal neutron fluxes increased. The thermal neutron flux at the tumor location decreased instead by 9 %. The irradiation time would then be longer (+7 %). The skin dose would increase by 11 % mainly due to the longer irradiation time. Another attempt was tried by attaching lithium pads at the beam exit with the hope to reduce the skin dose. Two lithium pads composed of natural lithium and enriched lithium were used. As a result, thermal neutron flux decreased by 30 % at tumor D80 location compared to the direct irradiation condition. The dose rates reduction for most critical organs was larger, 32 % for skin. Therefore, although the total irradiation time increased by 41 %, the critical organ doses become smaller. The increases of irradiation time could be compensated by increasing the reactor power. This patient was finally treated with lithium pads setup. For prescribed dose of 18 Gy (W) for 80% of the GTV, the total irradiation time was ~35 minutes for reactor power operated at 1.8 MW.

The optimum patient setups are different for tumors at difference depth. For superficial tumors, using patient collimator is better than direct irradiation. On the other hand, for deep-seated tumors, direct irradiation or attaching lithium pads at beam exit are better choices.

PI P1 03

The first clinical BNCT assessment through TCP calculations based on the novel concept of photon isoeffective dose

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Introduction

In a previous work we proved that the use of fixed relative biological effectiveness (RBE) factors leads to unrealistically high tumor doses. We also showed that the fixed RBE approach is not suitable to understand the observed clinical outcome of the Argentine cutaneous melanoma treatments in terms of the photon radiotherapy data. We then introduced a new formalism to compute photon-isoeffective doses and showed that the proposed approach derives values that are much more consistent to those considered therapeutic with single-fraction therapies. This work reports on the first application of the photon isoeffective dose concept to critically assess delivered doses to patients, and to optimize

upcoming treatments with the improved BNCT facility of the RA-6 reactor. The utilization of isoeffective doses opened for the first time the possibility to introduce a radiobiological figure of merit to score melanoma treatments. A tumor control probability model that takes into account non uniform doses is thus presented and applied to some clinical examples.

Materials and methods

Tumor isoeffective doses were computed for cutaneous melanoma cases selected from the phase I/II clinical trial, by applying the formalism and model parameters reported in [González & Santa Cruz, Rad. Res. **178** (2012) 609–621] for the human melanotic cell line Mel-J. Delivered treatments with the former clinical beam were reanalyzed in terms of the new facility. Isoeffective dose results for both the old and new scenarios were assessed in the light of standard photon therapy data. The tumor control probability model for single-dose melanoma treatments presented in González & Santa Cruz (2012) takes into account first order lesion repair. In this work, this is combined with the equivalent sub-volume model presented in [González & Carando, MMB **25** (2008) 171–184] to obtain a TCP model that in addition admits non uniform doses. Based on this radiobiological model and the calculated isoeffective doses, the expected number of controlled lesions for the original and reevaluated treatments was compared for each patient.

Results

An analysis of the tumor isoeffective doses for the three clinical cases reveals that these values are much lower than those derived from the fixed RBE approach, and are consistent with the doses commonly delivered in single-fraction therapies. Having established that isoeffective doses are more realistic estimates, they are used to compare the original and reevaluated treatments by means of the developed TCP model. Results show that the new BNCT facility would allow improving future melanoma treatments. Namely, the expected number of controlled lesions increases from 1/2, 7/13, and 5/7 to 2/2, 11/13 and 6/7 for the three analyzed patients, respectively.

Conclusions

The application of the photon isoeffective dose concept allowed introducing for the first time a radiobiological figure of merit as a credible scoring parameter for treatment assessments in BNCT. Particularly, this concept combined with the TCP model proposed in the present work lead to a meaningful quantification of the potential improvements in BNCT treatments due to the upgrades carried out in the RA-6 facility.

Pa P5 01

Deterministic parsing model of CBE factor for Intracellular ¹⁰B Distribution in Boron Neutron Capture Therapy

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Abstract

Deterministic parsing model of Compound Biological Effectiveness (CBE) in BPA-

mediated BNCT was proposed for intra-organ ^{10}B distribution. In defining the biological effects of the $^{10}\text{B}(n,\alpha)^7\text{Li}$ neutron capture reaction, CBE factor model is expressed; $CBE = CBE_0 (r_0 \leq r \text{ or } N \leq N_{th})$ and Where r and r_0 are distance between boron atoms and α range, N and N_{th} are boron concentration and threshold of ^{10}B concentration in tissues and tumour, The CBE_0 and F are obtained as 0.5 and 8 for normal tissues and for tumour, respectively. N and N_{th} are evaluated the bio-distribution of ^{10}B in normal tissues and tumour after injection and the CBE factor for normal tissues and tumor approximately within + 0.12 to -0.54 % high accuracy.

Pa P5 02

Geant4 study of BNCT mixed field energy deposit in an approximated healthy tissue geometry

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It is established that the clinical outcome of Boron Neutron Capture Therapy (BNCT) is related to the ^{10}B concentration and spatial distribution at cellular and subcellular level. This is due to complex interactions between the mixed radiation field of BNCT and the involved tissue structure. Therefore, different home-made Monte Carlo (MC) methods were developed to study the effects of different boron distributions in simple geometrical models of neoplastic tissue or capillary cells. Many physical parameters of the mixed radiation field were taken into account in these works: the most characterizing ones are cell hits, nucleus hits, hits by particles originating from inside the cell, hits from particles arising in neighbouring cells, energy deposit distribution in the nucleus and cytoplasm, Linear Energy Transfer (LET) distribution in the nucleus and cytoplasm.

The purpose of the present work is to study the parameters listed above in a new geometrical approach where real tissue structures such as: lung, muscle, bone, skin and hepatic tissue are reproduced with the highest possible precision. Boron distribution is set as uniform in different parts of the geometry, for example in the whole cell, only in the nucleus, only in the cytoplasm and concentrated in the cell surface. The study is computed with Geant4.10 which is a toolkit that can transport ionizing particles (electrons, protons, alpha, and lithium) through matter at low energies (few eV for electrons and protons).

The outcomes of these calculations are presented, comparing the mean parameters obtained in different tissues according to the different assumptions adopted concerning the boron distribution.

Pa P5 03

Weighted-Kerma/Fluence Factors for Monte Carlo calculations of the Biological Dose in BNCT

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Dose calculations for Boron Neutron Capture Therapy often rely on Monte Carlo simulations of neutron transport. Reference calculations as those of Goorley *et al.* [1] are based on the MCNP code for this purpose and make use of kerma/fluence factors which can be obtained from neutron cross section data. With this procedure one can calculate the absorbed (physical) dose. However, in BNCT treatment planning, the effective (biological) dose must be evaluated, at least approximately, in order to compare the values to the dose from conventional radiotherapy treatments. Usually this evaluation is done by means of effective factors which weight differently the main components of the dose, i.e. the thermal, fast neutron, gamma and boron dose. These factors are global factors obtained from radiobiology experiments, which depends on the tissue and the biological end-point considered in the measurements. In addition to this, and because the dose delivered (except for the gamma dose) is done by means of heavy charged particles which energy depends on the neutron energy, these factors would depend also on the neutron spectrum.

In this work we propose the use of energy-dependent weighted-kerma/fluence factors for Monte Carlo calculations of the dose delivered in BNCT treatments. They can be calculated analyzing the mean energy delivered by the charged particles produced for each neutron energy and the use of specific RBE factors for these secondary particles. These have been obtained using RBE-LET relationships from the literature [2] for heavy charged particles as protons or alphas, with the advantage that are better known than the own neutron RBE factors.

With this procedure one can tabulate energy-dependent weighted-energy factors for any particular dose component. The equations involved and the values obtained will be shown for a test case of medium: a 4-component ICRU soft tissue. From these values one can observe that the weighting factors for the fast neutron component (in the epithermal region) are smaller than those for the thermal ones, and they are increasing with the energy.

An application to the determination of the global weighting factors for the thermal, fast neutron and boron dose can be done by integration with the neutron spectrum and comparison to the components of the absorbed physical dose. Values for different biological end points will be shown.

[1] J.T. Goorley, W.S. Kiger III and R.G. Zamenhof, *Med. Phys.* 29, 145 (2002). [2] N.A.P. Franken, R. ten Cate, P.M. Krawczyk, J. Stap, J. Haveman, J. Aten and G.W. Barendsen, *Radiat. Oncol.* 6, 64 (2011).

Pa P5 04

Beta Enhancers: towards a new implementation for BNCT on superficial tumors

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Introduction

The Argentine clinical facility for treating superficial tumors is located at the RA-6 Research Reactor (Bariloche Atomic Center). The developed neutron beam, called hyperthermal, is composed of a mixture of thermal and epithermal neutrons and provides a thermal neutron flux peak of about 10^9 n.cm².s⁻¹ at approximately 1 cm depth. Due to the penetration of the beam, the total absorbed dose in the first few millimeters of the tissue is lower than in the maximum. Thus, the introduction of a suitable device over the irradiated geometry to allow a local increase of the surface dose without substantially perturbing the primary in-depth dose profile is considered in this work. Some materials for the proposed devices such as Rhodium, Silver and Indium have an interesting property: a high neutron capture cross section with short-lived activation products that decay emitting high energy beta particles. As beta radiation has a short penetration range in tissues, it can be used to compensate the superficial dose gradient and increase the absorbed dose of the BNCT treatment. Given that these particles do not discriminate between normal and tumor tissues, beta radiation-based devices are thought to be positioned on the anatomy surface, in a suitable configuration as close as possible to the target volume. These beta sources are called "Beta Enhancers", and takes advantage from backscattered thermal neutrons from the surface to a useful local contribution to the dose. This work presents the detailed analysis carried out to establish the feasibility of the proposal, in view of its effective application as a complementary tool in the Argentine BNCT treatment planning of superficial tumors.

Material and Methods

Beta Enhancers are modeled in Monte Carlo (MCNP), with their own characteristic particle sources of each case, to determine those candidates that minimize perturbation effects in the original therapeutic beam and significantly improves the local depth absorbed dose profiles. In order to validate these models, experimental measurements are carried out using radiochromic films and thermoluminescence detectors (TLD) in-depth of a solid phantom with Beta Enhancers positioned on its surface. The validated particle sources are then implemented in the simulation of selected nodular melanoma treatments of the Argentine BNCT patients. For computational dosimetry, patient anatomy is reconstructed by MultiCell program, because it has the capability of adapting voxels and tallies dimensions to the geometry description and dose calculation requirements.

Results

The simulations and its experimental correlations show good agreement, validating thus the computational models of the Beta Enhancers particle sources. Dose-Volume Histograms show the improvement of the local absorbed dose on the treated cancerous tissue. From 5 mm depth in tissue the effects related to the implementation of Beta Enhancers are not evident.

Conclusions

Beta Enhancers are a complementary tool to potentially improve the BNCT

treatment planning of superficial tumors cases, either because they allow compensating the inhomogeneity of the dose profile or increase the overall dose in the target. Thus, the dose is enhanced without significant perturbation to the primary neutron flux used in the BNCT treatment.

Pa P5 05

Near threshold ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction as a neutron source for BNCT

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${}^7\text{Li}(p,n){}^7\text{Be}$ is an endothermic reaction and working near the reaction threshold (1.88 MeV) has the advantage of neutron spectra with maximum energies of about 100 keV, considerably lower than at higher energies with the same reaction, or when using other reactions or the uranium fission spectrum. Since with this primary neutron energy it is much easier to obtain the energy spectrum needed to treat deep seated tumors by BNCT (about 10 keV), several groups have studied this reaction working near the reaction threshold as a neutron source for BNCT.

In the usual setup for near threshold ${}^7\text{Li}(p,n)$ there is a beam line for protons that ends in the target with its cooling system (not always considered). Behind the cooling system, a bolus of moderator material is used to reduce the neutron energies to about 10 keV and the patient is placed behind the bolus and aligned with the beam direction. The reason of this layout is that most of the neutrons of this reaction and particularly in the near threshold regime emerge in the forward direction, but this does not necessary lead to the optimal irradiation configuration. The neutrons emitted in forward direction are the most energetic ones of the reaction and other directions provide lower energies that can be moderated more easily. There are also other processes to be considered: the scattering in the bolus (and in the cooling system) not only reduces the neutron energy but also changes its direction, so that after the bolus the forward direction may not be the optimal.

In this work, the near threshold ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction is analyzed as a neutron source for BNCT by means of MCNP Monte Carlo transport simulations. The study is as function of the proton energy (from 1.925 MeV to 2.05 MeV), the bolus thickness and also as function of patient position. A realistic cooling system has been considered since its water has a drastic influence on the results. A-150 tissue equivalent plastic with enriched ${}^6\text{Li}$ carbonate has been considered as a bolus material that also absorbs the undesirable thermal neutrons. Patient position has been varied from 0 deg (the standard position) up to 160 deg referred to the beam direction. For patient angles up to 90 deg, the neutrons that reach the patient are those neutrons that could overcome the cooling system. In the case of angles greater than 90 deg, the useful neutrons are those that have been backscattered in the cooling system. Depth dose profiles in a Snyder phantom have been calculated for a 30 mA proton beam and the prescription was to maximize the irradiation time without exceeding 60 minutes, 11 Gy-Eq punctual

dose in healthy brain, 16.7 Gy-Eq in skin nor 7 Gy-Eq for the mean average dose.

Our results show that angles of 60 deg offer best tumor doses and that the lower the proton energy the better the results. Tumor doses up to 56.7 Gy-Eq have been obtained with a 1.925 MeV proton beam in a 55 min irradiation. The near threshold regime can lead to tumor doses comparable to those obtained with near resonance bombarding energy (~2.3 MeV), without the need of a beam shaping assembly and in a much simpler configuration.

Pa C1 01

Who benefits most of BNCT? – A review on literature data on the prognostic value of protein expression of amino acid transporter 4F2hc/LAT1

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Despite the undoubted clinical potential demonstrated through clinical trials in the past, the role of BNCT in modern tumour therapy remains marginal. Looking at available clinical data it becomes clear that there are patients who respond excellently to BNCT, while many others do not respond particularly well. It is therefore of utmost importance to select those patients for future clinical trials with the potential of a good response to the treatment.

Heterodimeric amino acid transport protein 4F2hc/LAT1 is known to be expressed in brain, testis, colon, ovaries, placenta, spleen, the blood-brain barrier, activated lymphocytes and fetal liver. Substrate transport by LAT-1 is of particular interest due its high expression in many tumours and it has been found to serve as a parameter to predict the progression of the disease for a number of prominent malignancies. It was especially shown that high protein expression of both the heavy chain (4F2) and the light chain (LAT1) is associated with poor outcome of the disease. Prognostic significance of both heavy chain and light chain is higher than for proliferation markers like ki-67, with which it hardly correlates. Furthermore, from this data it could be deduced, for a particular cohort of patients, which of those would profit the most from a therapy, where the 4F2hc/LAT1 amino acid transporter is specifically targeted.

4F2hc/LAT1 appears to play a crucial role in amino acid metabolism and protein synthesis in cells, where it regulates the uptake of bulky, neutral essential amino acids. Like a large number of L-phenylalanine derivatives, BPA has been confirmed to be a prominent substrate of 4F2hc/LAT1. Based on a literature review we are going to demonstrate the hidden potential lying within BPA-based BNCT for specific tumours, if protein expression of 4F2hc/LAT1 is used for the selection of patients for future BNCT trials.

Pa C1 02

BNCT for recurrent malignant gliomas, with the special combination of bevacizumab

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Since January 2002, we applied BNCT for malignant brain tumors with several new attempts. We have applied reactor-based BNCT for 45 cases of recurrent malignant gliomas (RMGs). We assessed the survival benefit of treating RMGs with BNCT. Unfortunately, the standard treatment for RMG has not yet been established. Therefore, evaluation of the survival benefit of BNCT for RMGs was difficult. To evaluate objectively this benefit in the low and high risk group of RMGs, we adopted the recursive partitioning analysis (RPA) classification for RMGs advocated by Carson et al. in a 2007 article in the Journal of Clinical Oncology. The article summarizes the results of 10 recent protocols of phase-1 and -2 trials applied by the New Approaches to Brain Tumor Therapy CNS Consortium (NABTT) for RMGs. When we published our initial results of BNCT for RMGs, survival data was analyzed using 22 consecutive cases of RMGs treated by BNCT from 2002 to 2007 [J Neuro-Oncology, 2009]. The median survival times (MSTs) after BNCT for all patients and for GBM as the histology at recurrence were 10.8 months (n=22; 95 % CI, 7.3 to 12.8 months), and 9.6 months (n=19; 95 % CI, 6.9 to 11.4 months), respectively. In our study, MST for the high-risk RPA classes (classes 3+7) was 9.1 months (n=11; 95 % CI, 4.4 to 11.0 months). Here, RPA class 3 consisted of cases ruled not to be GBM based on initial histology and KPS \leq 70%, while RPA class 7 consisted of cases judged as GBM at initial histology, patients 50 years of age or older, and/or patients using steroids to maintain ADL. By contrast, the original journal data showed that the MST of the same RPA classes was 4.4 months (n=129; 95 % CI, 3.6 to 5.4 months). BNCT showed a marked survival benefit for RMGs, especially in the high-risk group. Moreover, the median target volume on contrast MRI in our BNCT series was 42 ml, which could not be handled and treated by stereotactic radiosurgery.

The biggest drawbacks to the use of BNCT for RMGs are the occurrence of radiation necrosis and symptomatic pseudoprogression. RMG cases generally receive nearly 60 Gy X-ray irradiation prior to re-irradiation by BNCT. Therefore, even with tumor-selective particle radiation BNCT, radiation necrosis in the brain and symptomatic pseudoprogression may develop, especially in the recurrent cases. Occasionally radiation necrosis causes severe neurological deficits and sometimes endangers the patient's life. The key molecule in this pathology is vascular endothelial growth factor (VEGF). Bevacizumab, an anti-VEGF antibody, has recently been used for the treatment of symptomatic radiation necrosis. We have used bevacizumab in an attempt to treat and control the symptomatic radiation necrosis and the symptomatic pseudoprogression encountered after BNCT for RMGs with promising results [Neuro-Oncology, 2013 and Radiation Oncology, 2014]. Probably by use of bevacizumab for radiation necrosis and symptomatic pseudoprogression, we could update the MST data of high-risk group (RPA class 3+7), adding recent RMG cases treated by BNCT, as 11 months (n=19; 95% CI:7.8 to 12.4 months).

Also recently we use bevacizumab just after the BNCT for RMGs not to treat but to prevent radiation necrosis and pseudoprogression, and to expect the anti-tumor activity of this agent. Pilot study reveals a good response with this trial for RMGs. Now we start clinical trial with this new protocol for high risk RMGs. So far, we can use bevacizumab under the national health insurance in Japan. We thus conclude that the combination of BNCT and bevacizumab should improve the quality of life and prolong the survival of patients with RMG.

Pa C1 03

Clinical results of Boron neutron capture therapy for the patients with malignant meningioma

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Meningiomas are common intracranial neoplasms derived from arachnoidal (meningothelial) cells. Most meningiomas are benign (WHO Grade I), well-circumscribed, slow-growing, and curable by surgery depending on location. However, some meningiomas are clinically aggressive and can lead to significant complications and even death. Many, but not all, of these aggressive tumors are histological Grade II (atypical) or Grade III (anaplastic or malignant) tumors. Malignant meningioma is difficult pathology to control as well as glioblastoma. We tried to control malignant meningiomas by tumor-selective intensive particle radiation, boron neutron capture therapy (BNCT).

Since June of 2005, we applied BNCT for 31 cases (21 females and mean age is 59y) of malignant meningioma with 46 times neutron irradiation. They were 17 anaplastic, 2 papillary, 1 rhabdoid, 10 atypical meningiomas and 1 sarcoma transformed from meningioma. Median performance status was 90 in KPS and all cases had been treated with repetitive surgeries and radiotherapies. We applied ¹⁸F-BPA-PET before BNCT in 29 out of 31 cases.

The patients who received BPA-PET study prior to BNCT showed good BPA uptake as mean value of 3.8 in Tumor to Normal brain (T/N) ratio, which indicated more than 3.8 times higher particles were irradiated to tumor cells compared to normal cells and ensured successful treatments. Average tumor sizes were 52ml. Median survival time (MST) after BNCT is 22.4 (95 % CI: 12.4 - 44.0) months and MST after diagnosis as malignant is 59.6 (42.7 - 101.9) months. Clinical symptoms before BNCT, such as hemiparesis and facial pain, were improved after BNCT in almost all symptomatic cases. Major cause of death was systemic metastasis and CSF dissemination. Local tumor progression as a cause of death was observed in 2 cases. Radiation necrosis was observed in 6 cases but they were controllable except one case. Transient expansion of the enhanced lesion on contrast MRI was observed within 2 months after BNCT.

Boron neutron capture therapy is a new treatment concept and method that has already been used on malignant gliomas, including glioblastomas. Our study suggests that high-grade meningiomas may be an even better candidate for BNCT than those lesions. The meningiomas in our series were somewhat superficial (located on the surface of the brain), except for some specific situations at the skull base, which is advantageous to neutron penetration. With regard to BPA accumulation, high-grade meningiomas showed a good ratio of tumor to normal brain, even compared with malignant gliomas. In addition, judging from the rapid shrinkage of the mass, our assumption about the compound biological effectiveness of BPA for high-grade meningioma - which was assumed to be equal to that of glioblastoma - might have been an underestimation; the real value

might be higher than that for glioblastoma. If we can apply BNCT for high-grade meningioma as the initial radiotherapy or at least at the first recurrence, rather than at such advanced stages, more favorable results than those described in our study might be obtained, such as avoiding systemic metastasis or out-of-field recurrence.

Boron neutron capture therapy may be especially effective in cases of high-grade meningioma.

Pa C1 04

The ¹⁸F-BPA-PET SUV data as a prognostic factor for BNCT treatment failure: from clinical experience

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Introduction

BNCT is a tumour treatment based on thermal-neutron irradiation of tissues enriched with ¹⁰B, which according to the ¹⁰B(n, α)⁷Li reaction produces particles with high Linear Energy Transfer and short range. BNCT theoretically allows the preferential destruction of tumor cells while sparing the normal tissue, even if the cells have microscopically spread to the surrounding normal tissue. The success of BNCT ultimately depends upon the selective delivery of ¹⁰B-atoms to tumor cells. ¹⁸F-BPA-PET/CT is the standard to determine evaluation tumor cell ¹⁰B-atom uptake selectivity today. The purpose of this study is to investigate the prognostic value of pretreatment ¹⁸F-BPA PET SUV data on clinical response.

Material and Methods

According to our NCT01173172 clinical trial registered at the website www.clinicaltrials.gov, Every patient had received ¹⁸F-BPA-PET/CT before BNCT to determine tumor/normal tissues (T/N) ratios. Patients with T/N ≥ 2.5 were enrolled to receive two staged BNCT therapy. CT scan simulation and three-dimensional contouring were given to each patient. Prescribed dose of 20 to 25 Gy (Eq) to cover 80 % of gross tumor were planned by THORplan in two fractionations with interval of 30 days and given in Tsing Hua Open-Pool Reactor (THOR). The clinic outcome was evaluated by FDG-PET scan and MR scan. The data of clinical response, SUV heterogeneity and T/N ratio were collected for analysis.

Result

From 2009 to 2012, 12 patients with advanced local recurrent head and neck tumor were enrolled in this trial. 10 patients with follow-up more than two years were included in this study. There were 4 patients had CR and 6 patients had disease progression or recurrence. The overall average SUV heterogeneity data were 2.24 ± 1.28 (1.24-5.7). The disease progression group patients had higher SUV heterogeneity data compare to CR group patients, 2.64 ± 1.56 (1.68-5.7) vs. 1.65 ± 0.36 (1.24-1.97), respectively.

Conclusion

BNCT is an effective treatment for advanced local recurrent head and neck tumor with image CR rate of 40% in two year follow-up. SUV heterogeneity data might be a prognostic factor for clinic response.

Pa C1 05

A simple strategy to decrease the incidence of fatal carotid blowout syndrome after BNCT for head and neck cancers

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Background: Boron neutron capture therapy (BNCT) has attracted attention as a potential therapy for recurrent and advanced head and neck tumors. Currently, clinical trials of BNCT for head and neck cancers are being conducted to verify its usefulness [1]. However, carotid blowout syndrome (CBS) has become a serious complication of BNCT because of its associated life-threatening toxicity. Determination of the characteristics of CBS is important for the safe use of BNCT.

Patients and methods: Thirty-three patients (27 with recurrent head and neck cancer and 6 with newly diagnosed head and neck cancer) were treated with BNCT between 2003 and 2011 in our institution at the Kyoto University Research Reactor (KUR) and Japan Research Reactor No. 4 (JRR-4). The tumor/normal tissue boron concentration ratio (T/N ratio) obtained from ¹⁸F-boronophenylalanine (BPA)-PET was used for dose estimation before neutron irradiation and dose evaluation after BNCT with the treatment planning systems SERA or JCDS. Neutron irradiation was performed with an epithermal beam at a reactor power of 5.0 MW (KUR) or 3.5 MW (JRR-4) after intravenous administration of BPA in fructose solution at a dose of 500 mg/kg body weight. The tumor dose at the deepest part and the dose to both normal skin and mucosa were planned for more than 20 Gy-Eq and less than 15 Gy-Eq, respectively.

Results and discussion: Twenty-six of the 33 patients had recurrent cancer after irradiation. Eleven patients (7 with recurrence after irradiation) had carotid lesions in the irradiation field. Two patients (6%) developed CBS with an onset of about 3 months after BNCT that proved fatal; the survival time after CBS onset was 1 month, and both patients died. These two patients had widespread skin invasion and recurrence close to the carotid artery after irradiation. In contrast, CBS did not develop in patients with only postradiation recurrence or widespread skin invasion or lesions close to the carotid artery. The occurrence of CBS after radiotherapy for recurrent head and neck cancer was relatively high, approximately 10 %, in a previous report [2]. The incidence of CBS in our study was not quite as high as in that report.

Conclusion: BNCT is effective in head and neck cancer. However, widespread skin invasion and recurrence after irradiation are risk factors for CBS after BNCT.

Careful attention should be paid to the occurrence of CBS if the tumor is located adjacent to the carotid artery. The presence of skin invasion of recurrent lesions after irradiation at CBS onset is an ominous sign of lethal consequences. We must be aware of these signs to perform BNCT safely. This protocol for BNCT in recurrent and advanced head and neck cancer is promising in terms of decreasing the incidence of fatal CBS.

References

- [1] M. Suzuki, I. Kato, T. Aihara, et.al. Boron neutron capture therapy outcomes for advanced or recurrent head and neck cancer. *Journal of Radiation Research* 2014;55:146-153.
- [2] G. Yazici, T. Y. Sanli, M. Cengiz, et.al. A simple strategy to decrease fatal carotid blowout syndrome after stereotactic body reirradiation for recurrent head and neck cancers. *Radiation Oncology* 2013, 8:242.

Pa B2 01

Evaluation of micronucleation and viability of glioma cells *in vitro* neutron beams irradiated

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Boron neutron capture therapy (BNCT) is a promising approach for therapy of human brain tumor. The original accelerator-based epithermal neutron source was proposed and created in the Budker Institute of Nuclear Physics (BINP). Possibility to use this source for BNCT was tested on the model *in vitro*. Glioblastoma cell line U87 and normal human fibroblast cell line MRC-5 were incubated in a medium with and without b-[4-(10B)Boronophenyl]alanine (BPA) for 18 hours before irradiation. Cells in the culture plates were placed on the surface of the plastic phantom and inside the one at the depth of 3 cm. We proposed the transmission through the plastic to thermalize the neutrons; therefore the cells that were placed inside the phantom were irradiated thermal neutrons, whereas the cells on the surface phantom were treated by epithermal neutron beam (energy spectrum – from thermal to 100 keV, the average energy – 13 keV). Then during 2 hours, the irradiation of the two cell lines was performed using BINP neutron source. The cell viability at 1st, 3rd and 5th days after irradiation was determined by WST assay. The viability of cells that were irradiated by epithermal or thermal neutrons was not decreased compared with untreated cells at these time points. However, a clonogenic assay showed that, at 14th day after epithermal neutron irradiation, the surviving fractions of both pretreated with BPA and BPA-free cell lines were significantly decreased compared with untreated cells, while the clonogenicity of the cells that were treated by thermal neutrons depended on BPA pretreating. This irradiation significantly decreased the surviving fractions both tumor and normal cell lines that were pretreated with BPA compared with BPA-free cells despite the same amount of neutron radiations. The previous studies showed that irradiation induces formation of micronuclei, which are the evidence of mitotic catastrophe. Therefore, we carried out DAPI staining of irradiated cells. As it was observed, the epithermal

neutrons induced formation of micronuclei in both BPA pretreated and BPA-free cell lines, whereas thermal neutrons resulted in the micronucleation only in the BPA pretreated cells. According our results we conclude that: i) BINP neutron source can be used for BNCT; ii) fast neutrons are toxic for the cells *in vitro*; iii) the cytopathic effect of thermal neutron beam depends on the accumulation of BPA.

Pa B2 02

Analysis of cell-death response and DAMPs after boron neutron capture reaction in human cancer cells

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We have been studying the molecular mechanisms involved in the boron neutron capture reaction (BNCR). To understand the early response after BNCR in human cancer cells, transcriptome and proteome analyses were performed six and twenty-four hours after thermal neutron beam irradiation to oral squamous cancer SAS cell line at the dose of 24 Gy-eq under boronophenylalanine (BPA) (+) and BPA(-) conditions. Genes involved in cell death, transcriptional regulation, and inflammatory and immune responses were increased after BNCR; activating transcription factor (ATF3), early growth response 1 (EGR1), colony stimulating factor 2 (CSF2), interleukin-6, and interleukin-8 were upregulated. Proteome analysis was performed using two dimensional-polyacrylamide gel electrophoresis and mass spectrometry. Proteins involved in RNA processing, transcription, DNA repair, immune response, and endoplasmic reticulum function were found to be increased in the cells. Secreted proteins after BNCR were detected and being studied with the proteome and ELISA analyses. Among them, the leakage of high mobility group box 1 (HMGB1), one of the proteins of damage-associated molecular patterns (DAMPs), was increased in an irradiation-dose dependent manner in the culture medium. The results suggest that diverse irradiation responses including DAMPs could be induced after BNCR reaction as an early response.

Pa B2 03

Three In One: A Multifunctional Antitumor Sensitizer for Photodynamic, Boron Neutron Capture and Proton Therapies

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Physical methods in antitumor treatment are frequently used in combination (simultaneous or sequential) to achieve maximal effect. Therefore, the compound capable of sensitizing tumor cells to different types of energy (light, ionizing radiation, thermal neutrons) would be applicable in more than one therapeutic modality. Extensive worldwide studies yielded a variety of chemically modified natural and synthetic porphyrins and chlorins. The tetrapyrrole macrocycles in these compounds can be modified by the addition of metal cations into the coordination sphere. Furthermore, the functional groups at the periphery of the macrocycle are convenient for substitutions for a variety of chemical moieties that differ in size, volume and electric charge.

A decade-long work by our group has demonstrated that boron polyhedra conjugated to the periphery of tetrapyrrole macrocycles can improve the efficacy of photodynamic therapy (PDT) in animal models. This effect has been attributed, in part, to membrane localization of the sensitizer conferred by boronation. Further structural optimization included the addition of 16 fluorine atoms into 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin. Importantly, we substituted ¹¹B atoms in the carborane cages for the enriched boron-10. The resulting compound, {5,10,15,20-tetrakis[4-(1-carba-closo-dodecaboran-1-yl)tetrafluorophenyl]-17,18-dihydro-porphyrin} sodium (**1**) showed a good water solubility, fast intracellular intake and cytoplasmic accumulation, as well as low-to-null dark cytotoxicity. Compound **1** formed no stable complexes in vitro with the blood plasma transporters such as albumin or low density lipoproteins (as shown by spectroscopy and molecular docking), suggesting that in the body **1** can act in a free (unbound) form. Compound **1** potently (at low micromolar concentrations) sensitized the s.c. transplanted C6 glioma cells (a Balb/c-nu/nu murine model) to PDT and BNCT. Counterintuitively, **1** also increased the efficacy of proton therapy. Most importantly, after the administration of **1** a combination of PDT followed by BNCT or protons resulted in a substantial shrinkage of the tumor node (up to its total disappearance) and a statistically significant increase in the life span of tumor bearing animals. The non-invasive tumors were more susceptible to the combinations of PDT with ionizing therapies than the tumors that invaded the surrounding muscle. No signs of general toxicity (i.e., behavioral or nutritional habits, hair or weight loss) were registered in mice injected with **1** and then treated with the above mentioned combinations for at least 3 weeks post irradiation.

These results provide evidence that structural optimizations of known chemical classes may confer valuable characteristics to compounds initially designed for one particular therapeutic modality. Indeed, **1** emerges as a perspective antitumor compound with triple potencies: at well tolerated doses of this photoradiosensitizer the antitumor effects of PDT, BNCT and proton irradiation are synergistic.

Pa B2 04

The influence of the p53 status for biological effects of the glioblastoma cells following boron neutron capture therapyKeiko SEKI, Yuko KINASHI, Sentaro TAKAHASHI and Koji ONO¹Research Reactor Institute, Kyoto University, Kumatori-cho, Sennann-gun, Osaka 590-0494, Japan

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Introduction

Cell death is a key biological effect in the radiation therapy of cancer. A tumor suppressor gene, p53 has an important role in the cell death, and is known to be mutated in many types of cancer, especially in glioblastoma. We studied the relationship of p53 gene with biological effects of BNCT in two types of human glioblastoma cells; A172 with wild type of p53, and T98G cells with mutant type of p53.

Materials and Methods

The human glioblastoma cells, A172 and T98G were purchased from Riken BRC Cell Bank. A172 cells have wild type of p53, and T98G cells have mutant type of p53. These cells were irradiated with the neutron mixed beam at the Heavy Water Facility of the Kyoto University Research Reactor (KUR). BPA(boronophenylalanine) was added into the medium at the final concentration of 14µl/ml one hour before neutron irradiation. After irradiation, the biological effects in the glioblastoma cells were studied three methods; 1) Cell survival assay by the colony formation assay, 2) DNA-DSB(double strand break) focus assay by immunofluorescence staining of 53BP1 foci in the cells, 3) Apoptosis detection with TUNEL method.

Results

The cell survival assay showed that the cell killing effect of neutron for A172 was greater than T98G without BPA. Survival parameter D10 doses were 1.6Gy in A172 and 5.2Gy in T98G without BPA. However, the difference in the radiosensitivity between two glioblastoma cells reduced by neutron irradiation with BPA addition. Survival parameter D10 doses were 0.8Gy in A172 and 1.1Gy in T98G with BPA. The DNA-DSBs focus assay by immunofluorescence staining of 53BP1 foci showed that there was little clear difference between both brain tumor cells, so the results suggested that the DNA damages of irradiated glioblastoma cells slightly depend on p53 functions. From apoptosis detection by TUNEL method, T98G showed lower apoptosis induction rate than A172. The apoptosis incidence in the both two cells with BPA was observed higher than without BPA.

Conclusion

This study revealed that BNCT caused cell death in the glioblastoma cells, regardless of mutant p53 status. In addition, it seemed that T98G may have p53-independent apoptosis or the so-called non-apoptotic cell death that include autophagic generation and non-lysosomal disintegration following BNCT.

Pa B2 05

OPTIMIZATION OF BORON NEUTRON CAPTURE THERAPY (BNCT) FOR THE INDIVIDUAL TREATMENT OF CUTANEOUS MELANOMACarpano M¹, Nieves S², Santa Cruz G², Olivera MS², Perona M¹, Rodriguez C¹,

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BNCT is a radiation therapy that provides a way to destroy tumor cells without harming surrounding normal tissue significantly. The success of this therapy depends primarily on the ability of the boron compound to concentrate selectively in the tumor. In our laboratory, in order to optimize the individual application of BNCT to the cutaneous melanoma, we performed different studies. Previously we have shown that different human melanoma cell lines have different patterns of boronophenylalanine (¹⁰BPA) uptake. On the other hand, mice implanted with one of these cell lines developed tumors with different biological and physical characteristics, and we found a positive correlation between BPA uptake, percentage of viable cells and tumor temperature. The aim of these studies was to evaluate if the observed correlation between intratumoral boron content, temperature and viability translates into a better response to neutron irradiation.

Materials and Methods

60 male NIH nude mice were implanted subcutaneously (sc) in the right flank with 3×10^6 of Mel J cells. The animals were divided into 3 groups: 1) Control: without irradiation and BPA; 2) NCT: irradiated with the neutron beam; 3) BNCT: irradiated with the neutron beam plus BPA (350 mg/kg b.w). Each mouse was individualized and was transported by plane to the Bariloche Atomic Center (CAB) to be irradiated in the thermal neutron beam of RA6 (Flux: $4.96 \cdot 10^8$ n/cm²). Animals were anesthetized s.c. with diazepam and ketamine (200 mg/kg b.w) and irradiated in groups of 8 for 37.0 ± 0.5 min. Tumor growth and tumoral histology were evaluated for 40 days post treatment. Body and tumor temperatures of each mouse were measured by infrared thermography, pre and post treatment, as a non invasive indicator of boron uptake and histology.

Results

Tumor continues to grow in the animals of the Control group, reaching a value of 30.81 in the relative tumoral volume at 40 days post treatment. At the same time, the NCT group reached a relative tumor volume of 28.72, while the BNCT group showed complete stop in the tumor growth during the first 20 days after treatment, but reaching an average value of relative volumen of 3.64 at the 40 day. Total physical absorbed doses were 13.4 ± 5.1 % cGy/min for BNCT group and 5.8 ± 1.8 % cGy/min for NCT group. Animals with lower differences between the body and the tumoral temperatures and higher tumor temperature had a better response to treatment.

Conclusion

The temperature measurement by termography in each mouse could be used as a predictive marker of therapeutic success for optimizing individual BNCT therapy.

PS2 B 01

BNCT as a potential therapy for rheumatoid arthritis: bio distribution study of BPA and GB-10 in a model of antigen-induced arthritis in rabbitsTrivillin VA^{1,2}, Abramson DB³, Bumaguin GE³, Bruno LJ³, Garabalino MA¹, Monti Hughes A¹, Heber E¹, Feldman S^{3,4}, Schwint AE^{1,2}.¹Comisión Nacional de Energía Atómica; ²CONICET; ³LABOATEM, Universidad Nacional de Rosario; ⁴CI, Universidad Nacional de Rosario, Argentina**Introduction**

Experimental and clinical studies have demonstrated the therapeutic efficacy of BNCT for several tumors with no significant radiotoxicity in normal tissue. New applications of BNCT such as the treatment of rheumatoid arthritis (RA) by inducing selective damage in the pathological synovium are being explored. The aim of the present study was to design a tissue sampling procedure in a model of antigen-induced arthritis (AIA) in female *New Zealand* rabbits and perform biodistribution studies with BPA and GB-10 to determine boron concentration in synovium (target tissue) and clinically relevant normal tissues.

Materials and methods

AIA was induced by 2 successive intra-dermal immunizations with ovalbumin emulsion (OVA) (1 mg/ml), 1:1 complete Freund's adjuvant, and 15 days apart. An intra-articular (ia) injection of OVA (1 mg/ml) was performed 5 days later. Approximately 40-50 days after the first immunization (chronic phase), the rabbits were used for biodistribution studies employing the following protocols: **a)** 0.5 ml BPA 0.05M (0.26 mg ¹⁰B) intra-articular (ia) **b)** 0.5 ml GB-10 (5 mg ¹⁰B) ia **c)** 0.5 ml BPA 0.14M (0.7 mg ¹⁰B) ia **d)** 0.5 ml de GB-10 (50 mg ¹⁰B) ia **e)** BPA (15.5 mg ¹⁰B/Kg) intravenous (iv) **f)** GB-10 (50 mg ¹⁰B/Kg) iv and **g)** BPA (15.5 mg ¹⁰B/Kg) iv + GB-10 (50 mg ¹⁰B/Kg) iv. At different post-administration times (13 to 85 min. for ia administration and 3 h for iv administration), samples of blood, synovium, cartilage, tendon, muscle and skin were taken and processed for boron measurement by ICP-MS.

Results and Conclusion

The ia administration protocols at <40 min post-administration both for BPA and GB-10, and the iv (systemic) administration protocols for GB-10 and [GB-10 + BPA] exhibit therapeutically useful boron concentrations (>20ppm) in the pathological synovium. However, it would be contributory to enhance selective boron uptake in pathological synovium versus cartilage since cartilage is expected to be the dose-limiting healthy tissue.

PS2 B 02

Significance of Combined Treatment with Bevacizumab in Boron Neutron Capture Therapy in Terms of Local Tumor Response and Lung MetastasisS. Masunaga¹, Y. Sakurai², K. Tano¹, H. Tanaka², M. Suzuki³, N. Kondo³, M. Narabayashi³, T. Watanabe³, Y. Nakagawa³, A. Maruhashi², K. Ono³

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Objectives

To evaluate the effect of bevacizumab on local tumor response and lung metastatic potential in boron neutron capture therapy (BNCT), referring to the response of intratumor quiescent (Q) cells.

Methods

B16-BL6 melanoma tumor-bearing C57BL/6 mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all proliferating (P) tumor cells. The tumors received reactor thermal neutron beams following the administration of a ¹⁰B-carrier (*L*-para-boronophenylalanine-¹⁰B (BPA) or sodium mercaptoundecahydrododecaborate-¹⁰B (BSH)), with or without the administration of bevacizumab, and further in combination with an acute hypoxia-releasing agent (nicotinamide) or mild temperature hyperthermia (MTH, 40°C for 60 min). Immediately after the irradiation, cells from some tumors were isolated and incubated with a cytokinesis blocker. The responses of the Q and total (= P + Q) cell populations were assessed based on the frequency of micronuclei using immunofluorescence staining for BrdU. In other tumor-bearing mice, 17 days after irradiation, lung metastases were enumerated.

Results

Three days after bevacizumab administration, the sensitivity of the total tumor cell population after BPA-BNCT had increased more than after BSH-BNCT. The combination with MTH, but not with nicotinamide, further enhanced total tumor cell population. With or without a ¹⁰B-carrier, MTH enhanced the sensitivity of the Q cell population. With or without irradiation, the administration of bevacizumab showed some potential to reduce the number of lung metastases, as well as nicotinamide treatment, especially in BPA-BNCT compared with BSH-BNCT.

Conclusions

The use of BSH as a ¹⁰B-carrier in combination with MTH is thought to be advantageous and promising in terms of local tumor response in BNCT because MTH reduces the difference in radiosensitivity between radiosensitive total and radioresistant Q cell populations. BPA-BNCT in combination with nicotinamide and/or bevacizumab treatment may show a little greater potential to reduce the number of lung metastases from the primary solid tumor. In BNCT, bevacizumab has the potential to sensitize total tumor cell populations and cause a decrease in the number of lung metastases to a similar level to nicotinamide. Finally, it was elucidated that control of the chronic hypoxia-rich Q cell population in the primary solid tumor has the potential to impact the control of local tumors as a whole, and that control of the acute hypoxia-rich total tumor cell population in the primary solid tumor has the potential to impact the control of lung metastases from the primary tumor.

PS2 B 03

RESEARCH OF INFLUENCE OF BORON-CAPTURE REACTION ON TRANSPORT PROTEINS OF HUMAN BLOOD SERUM

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Influence of epithermal neutrons irradiation on drug-binding ability of human blood serum proteins at presence of borate buffers has been investigated. As a source of boron was used borate buffer pH 7.4. For estimation of neutron irradiation influence on blood serum proteins we chose 50 mM concentration of borate buffers (with contents of ^{10}B 106.49 $\mu\text{g}/\text{ml}$ - that in 3.55 times above of therapeutic dose (in references the effective concentration of ^{10}B in irradiated tumour about 30 $\mu\text{g}/\text{g}$). Application of borate buffer as a source of boron in the irradiated sample does not influence of binding of pharmacological preparations with blood serum proteins. It in turn allows changing concentration of boron in the investigated sample in the wide range.

Also as well as in case of with background irradiation (without boron) we found, that the irradiation by epithermal neutron beam of human blood serum proteins in 50 mM borate buffer (with concentration $^{10}\text{B} = 106.49 \mu\text{g}/\text{ml}$) changes characteristics of binding of tritium labeled preparations with transport serum proteins in various degree. Thus, it is observed both reduction of binding, and increase of binding that testifies to functional activity of binding sites of albumin molecule. The percent of changes of binding is quite comparable with changes at irradiation in absence of boron. In addition, it is not observed the full denaturation of ligand-binding sites of albumin. Obtained data are in agreement with [1] showing, that for full protein denaturation more powerful doses of a neutron irradiation are necessary. From this, it is possible to assume confidently enough, that the therapeutic irradiation by epithermal neutron beam in whole does not render destroying influence on binding ability of transport proteins of human blood serum both at presence ^{10}B , and in its absence.

1. *Protection and regeneration at radiation damages. Moscow, "Science" 1966.*

PS2 B 04

Detection of plasmid strand breaks in boron neutron capture reaction

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The mechanism of DNA damage caused by boron neutron capture therapy (BNCT) has not been revealed in detail. The aim of our study is to provide simple model for investigating DNA fragmentation by BNCT. TE buffered liquid plasmid samples were mixed with boron and irradiated. Agarose gel electrophoresis was used to assess DNA forms. We detected suitable methods by varying concentration of DNA sample and boron. Also the effects of different types of plasmid and different gels were examined.

PS2 B 05

Therapeutic Efficacy of Boric Acid-Mediated Boron Neutron Capture Therapy for Liver Tumors in a VX2 Multifocal Liver Tumor-bearing Rabbit Model

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Introduction

Boron neutron capture therapy (BNCT) has been proposed for treating multiple, unresectable liver tumors, but a suitable boron drug must be developed to improve its therapeutic efficacy. Our previous studies have shown the high therapeutic efficacy of boric acid-mediated BNCT in N151 hepatic tumor-bearing SD rats. The aim of this investigation is to evaluate the therapeutic efficacy of BA-mediated BNCT in a second animal model, the VX2 multifocal liver tumor-bearing rabbit model.

Materials and Methods

A VX2 multifocal liver tumor-bearing rabbit model was established and ¹⁰B-enriched boric acid (99 % ¹⁰B) was used as the boron drug. The tumor-bearing rabbits were divided into three groups - the BNCT-treated group, the NCT group and the tumor control group. Pharmacokinetic analysis was performed to determine the optimal time interval for neutron irradiation. Boron concentration was measured by ICP-AES. The microdistribution of boron in tumor-bearing liver was investigated by neutron capture autoradiography. The rabbits that were intravenously injected with boric acid (50 mg ¹⁰B/kg BW) were irradiated with neutrons at the Tsing Hua Open Pool Reactor 35 minutes following the BA injection. The physical dose was calculated using MCNP (Monte Carlo N-particle) code. Ultrasound imaging and computed tomography scanning were conducted to determine the tumor size and the blood supply of tumors.

Results

Pharmacokinetic analysis revealed that the blood boron concentration was 60 ± 5 ppm 35 minutes following the administration of BA, and slightly declined (~3 ppm) from 35 to 65 minutes. In this period, according to the autoradiographical analysis, the number of tracks in the tumor and the tumor vessels was about 2.5 times that in a normal liver tissue. Therefore, neutron irradiation was performed 35 to 65 minutes following BA injection. Eight rabbits with 23 tumors were treated with two-fraction BNCT. The physical dose that was administered to the tumors ranged from 6 to 16 Gy in the first BNCT and 6 to 11 Gy in the second BNCT. Although body weight loss was detected in rabbits that had undergone BNCT, this weight was recovered within seven to ten days. An obvious reduction in tumor size (35 to 60 %) and in the blood flow around the tumor were detected by ultrasound scanning 22 days after the first fraction of BNCT treatment (that was relative to 1 day before the second BNCT). The size of the tumors continued

to decrease thereafter and the blood flow around the tumor was undetectable 30 days after the second BNCT. The therapeutic response that was detected by ultrasound scanning, described above, was consistent with the results of the CT scan. Rabbits were sacrificed on the 145th day following the first fraction of BNCT for the histopathological investigation. Massive tumor cell necrosis and mineralization were observed in the central area of the tumor mass, forming a thick granuloma, or a granulomatous scar with calcification of the tumor mass were noted in the liver. Histopathological examination revealed that the tumor was completely cured. Owing to tumor overgrowth, rabbits in the NCT group and the tumor control group were sacrificed humanely 30-60 days after tumor inoculation.

Conclusion

BA-mediated BNCT can deliver curative radiation dose to tumors and the tumor vessels while sparing the normal liver tissue. Therefore, this method has the potential to provide a better way for liver tumor therapy. More efforts are under way to study the detailed mechanisms of BA-mediated BNCT.

PS2 B 06

Continuous infusion of low-dose BPA to maintain a high boron concentration in tumor and narrow down the range of normal tissue to blood boron ratios for BNCT in a mouse model

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Introduction

The boron dose that is used in boron *neutron capture therapy* (BNCT) depends on the concentration of the boron drug in the targeted tumor, but because of inaccessibility of the tumor, boron concentrations are usually measured in the blood. The design of a drug use process to obtain the steady-state plasma levels of boron by IV infusion will be *beneficial* in the accurate calculation of the boron dose in BNCT. In this study, a boron drug (BPA), was administered by intravenous infusion, and then low-dose continuous infusion to keep the boron concentration high in the tumor, and to narrow down the range of ratios of the boron level in normal tissue to that in blood.

Materials and Methods

Human oral squamous cell carcinoma SAS cells were implanted subcutaneously into the right forelimb in BALB/c mice. Mice were administered BPA at a dose of 20 mg/kg/min via the tail vein for 20 min as the first infusion, and then separated into continuous infusion and non-continuous infusion groups. In the continuous infusion group, the BPA-treated mice were given a continuous infusion of BPA at a dose of one tenth the dose in the first infusion. Continuous infusion was performed for *four durations* (15, 30, 45 and 60 min). After each duration, mice were sacrificed to collect samples of the tumor, normal tissue and blood. In the non-continuous infusion group, mice were sacrificed for the collection of samples at 15, 30, 45 and 60 min *after the first infusion*. The boron concentration in the collected samples was analyzed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES).

Results

In the continuous infusion group, boron concentrations in the tumors were 34.27 ± 1.90 , 38.03 ± 5.47 , 43.21 ± 1.93 , and 42.65 ± 1.72 ppm; the T/N ratios were 1.83, 1.93, 1.92 and 1.91, and the T/B ratios were 1.16, 1.24, 1.41 and 1.44 at 15, 30, 45 and 60 min of continuous infusion, respectively. In the non-continuous infusion group, the boron concentrations in the tumors were 23.65 ± 4.57 , 25.79 ± 5.28 , 26.68 ± 2.08 and 31.20 ± 6.12 ppm; the T/N ratios were 1.05, 1.15, 1.23 and 1.52, and the T/B ratios were 1.31, 1.98, 3.56 and 4.48, at 15, 30, 45 and 60 min respectively, after the first infusion. The N/B ratios in the continuous infusion group were in the range 0.63-0.75 and those in the non-continuous infusion group were in the range 1.26-2.94 in the tested intervals. When the T/B ratio was assumed equal to the T/N, the percentage errors of boron dose estimation at 45 and 60 min in continuous infusion group were 36.62 % and 32.52 %, respectively, whereas those at 45 and 60 min following the first infusion step for the non-continuous infusion groups were -65.44 % and -66.09 %, respectively.

Conclusion

Continuous infusion of BPA at a dose rate of one tenth of the *first* infusion can maintain tumor boron concentration at a level higher than that achieved in groups with non-continuous infusion. A stable and narrow range of N/B ratios can be obtained, which are important for accurate calculations of doses for BNCT.

PS2 B 07

Additive effect of BPA and Gd-DTPA for application in accelerator-based neutron source

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Introduction

In neutron capture therapy, the therapeutic effect of the boron compound is based on alpha particles produced by the $B(n, \alpha)$ reaction while the gadolinium compound effect is gamma rays derived from the $Gd(n, \alpha)$ reaction. Gadolinium has a large neutron capture cross-section. However, due to the fast decrease in therapeutic concentration, it has not been used in neutron capture therapy.

It has been proposed to use a proton accelerator for neutron production instead of a nuclear reactor. One of the features of the accelerator neutron source is short irradiation time, which is advantageous for gadolinium neutron capture therapy. If gadolinium is administered simultaneously with boron and is irradiated with neutrons, it might become a source of additional local gamma rays.

In the present study we evaluated the additive effect of boron and gadolinium using the reactor-based neutron source for further application in accelerator-based neutron source.

Materials and Methods

BPA and Gd-DTPA were used as target compounds for neutron capture therapy. In the *in vitro* study both substances were added to the medium containing U251

(human glioma) or CT26 (mouse carcinoma) cells. The cells were irradiated at the neutron reactor at Kyoto University, and the colony formation assay was done. In the biodistribution study C6 (rat glioma) subcutaneous model was used. BPA and Gd-DTPA were administered in tail vein of the tumor-bearing Wistar rats, and the change in compound concentration in the tumor tissue was measured at different time intervals.

Result and discussion

After neutron irradiation the survival of both types of tumor cells with additional 5 ppm of Gd-DTPA decreased to 1/10 compared to the cells with boron only. Gadolinium has six stable natural isotopes, ^{154}Gd , ^{155}Gd , ^{156}Gd , ^{157}Gd , ^{158}Gd , and ^{160}Gd . We applied clinically used gadolinium compound, containing about 15% of ^{157}Gd , which reacts with neutrons. Thus, the amount of ^{157}Gd in 5 ppm of Gd-DTPA might be less than 1 ppm, which is responsible for additive effect. Higher concentration of ^{157}Gd might be more beneficial in combined neutron capture therapy.

In the biodistribution study, the concentration of boron in subcutaneous tumor tissue did not change significantly, though the concentration of gadolinium decreased from 13.2 ± 2.1 to 4.1 ± 1.2 ppm during first 60 minutes after injection. There was no difference in gadolinium concentration between the groups with independent and simultaneous BPA and Gd-DTPA administration.

Conclusion

Combined BPA and Gd-DTPA administration improved the neutron capture therapy effect in vitro in comparison with BPA only. The biodistribution study allowed determining more eligible time intervals for neutron irradiation after both compounds injection. Further studies are required to estimate the most effective ratio of boron and gadolinium for neutron capture therapy.

PS2 B 08

Experimental trial of establishing brain necrosis mouse model using proton beam

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Brain necrosis is the most serious late adverse event that occurs after 6 months following radiation therapy. Effective treatment for this irreversible brain necrosis has not been established yet. Brain necrosis often occurs even after BNCT, which is the tumor selective radiation therapy, for recurrent malignant glioma or meningioma. This study tries to establish brain necrosis mouse model using proton or helium beam.

The right cerebral hemispheres of BalbC57 mouse brains were irradiated at doses of 40, 50, 60 Gy with charged particles (70 MeV proton and 220 MeV helium;

5mm spread-out Bragg peak). The spread-out Bragg peak used here successfully retained its high-dose localization in the defined region.

After irradiation, examinations of the magnetic resonance imaging (MRI) and histopathology were conducted. In the case of 60Gy irradiation, after 2-3 months, change in the apparent T2 high intensity in the white matter of the right cerebral hemispheres of the side that has been irradiated was observed in the MRI, and almost all mice died within 2-3 months. Histological examination showed marked edema, increased micro-vessels and extension of the vein, in the same area which match the white matter portion of the exhibited T2 high intensity in MRI. On the other hand, in the case of 40Gy, no significant changes were observed both in MRI and histopathology at 6 months after irradiation. At 10 months after irradiation, even 40 and 50 Gy irradiated groups, showed mix intensity in MRI. Histopathological examinations have been currently in progress.

We believe that our experimental model for irradiating a restricted region of mouse brain using proton or helium beam is a good model for analyzing late adverse event caused by radiation. Next, we are now trying some drugs which might control these late adverse event.

PS2 B 09

Localized Dose Delivering by Ion Beam Irradiation for Experimental Trial of Establishing Brain Necrosis Model

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Introduction

Occurrence of radiation necrosis is one of the most serious late adverse events after a BNCT irradiation for brain tumor treatment. To determine mechanisms underlying the radiation necrosis, establishment of rodent model has been attempted by several groups. Our group has been performing experimental trials to establish such a model using accelerated ion beams of proton or helium, which is a promising way to deliver high radiation dose uniformly in a local volume of rodent brain. In this report, beam shaping techniques and characteristics of irradiation field used in the experimental trials were described.

Beam shaping techniques

Proton or helium beams, accelerated up to 70 MeV and 220 MeV, respectively, by synchrotron at the Wakasa Wan Energy Research Center, were used for irradiation experiments. These beams were shaped by spreading out the Bragg peak and by diverging and collimating the pencil beam to form a uniform dose distribution in both depth and lateral directions.

A multi-step degrader made by stack of Mylar sheets was used to form a spread-out Bragg peak (SOBP). The degrader was prepared to have several steps with

thickness increment of 500 μm for proton beam, and 300 μm for helium beam. Each step was used in series with different weight of beam current. The weight of each step was determined based on a calculation of mono-energy Bragg curves. Reaching depth of SOBP can be adjusted by minimum thickness of the degrader.

A pencil beam delivered from the synchrotron was broadened by scattering plate enough to cover a target region. Then the diverged beam was collimated to fit to the target shape.

Characteristics measurement of irradiation field

Characteristics measurement was performed for an irradiation field formed by using these beam shaping techniques. Depth dose distribution of mono-energy beam was measured by a plane-parallel ionization chamber at a few points of depth direction. The measured distribution showed a good agreement with calculated one. The result may support that the SOBP has uniform distribution although the direct measurement was not performed for the SOBP. Two dimensional dose distributions was measured by imaging plates for rectangle fields shaped by collimator with opening of 10 \times 10 mm for whole brain irradiation and 10 \times 5 mm for cerebral hemisphere irradiation. The measured results showed uniform 2-D distribution with small penumbra width.

Conclusion

It was confirmed that the beam shaping techniques adopted in this study could be used to deliver high radiation dose uniformly in a local volume of rodent brain.

PS2 B 10

Prospects of intercellular complexes with gadolinium application in Binary Radiotherapy

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The efficacy of cancer Binary Radiotherapy (BRT) both neutron capture therapy (NCT) and contrast enhanced radiotherapy (CERT) is highly dependent on the ratio of special drug concentration in the tumor and the surrounding normal tissues (T/N ratio). By the moment attempts of developing special tumor-seeking drugs capable to provide necessary for BRT T/N ratio were of no success. However for particular types of tumors some their pathomorphological properties caused by tumorigenesis such as blood barrier disruption in case of brain tumors or hypervascularisation of some types of tumors can be used. We performed comparative *in vivo* visualization of disodium gadopentetate (Gd-DTPA) in three different murine transplanted tumors. Obtained results showed different rate of accumulation in different tumors. Tumor with the highest rate of Gd-DTPA accumulation was chosen to study whether the absorbed amount of gadolinium is enough for effective BRT. Calculations of many researchers show that therapeutic efficacy of Gd-NCT and CERT of the same origin and is mostly due to Auger-electrons and electrons of conversion that is why x-ray irradiation was used to study the therapeutic significance of Gd-DTPA passive accumulation

in hypervascularised transplanted tumor.

Materials and Methods

C57Bl/6 mice with transplanted carcinoma Ca755 were used in the study. Animals were divided into three groups. 1st group undergo no treatment. 2nd group was irradiated with 10 Gy of x-ray. Animals in 3rd group were administered with 0,3 ml of 0,5M water solution of Gd-DTPA, containing 23 mg of gadolinium and irradiated with the same dose of x-ray. Administration of Gd-DTPA solution was performed with single systemic injection. Irradiation was performed with x-rays machine with the voltage of 200 kV and dose rate of 1,3 Gy/min. Antineoplastic efficacy was estimated by measuring tumor volume and survival of mice.

Results

Tumor growth delay for experimental group was 12 days whereas in both control groups no tumor growth delay was observed. Life span median was 22 days, 36 days and 43 days for 1st, 2nd and 3rd group respectively. In 3rd group 25 % of animals have full tumor regression whereas in both control groups no tumor regression was observed.

Conclusion

Obtained results show that systemic injection of intercellular drug with gadolinium prior irradiation with x-ray provides enough amount of gadolinium in highly vascularized tumors and lead to significant increase of antineoplastic effect of x-ray irradiation. Taking into consideration similar physical processes causes therapeutic efficacy of Gd-NCT and CERT and very high value of thermal neutron absorption cross section of ¹⁵⁷Gd isotope, antineoplastic effect of Gd-NCT with systemic administration of intercellular gadolinium containing drug could be even more significant.

PS2 B 11

Novel multi-linked mercaptoundecahydrododecaborate (BSH) fused cell-penetrating peptide accelerated boron neutron capture therapy (BNCT)

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Introduction

The protein transduction domains (PTDs) such as that in TAT protein from HIV-1 are capable of mediating the transfer of proteins across the plasma membrane into nearly all eukaryotic cells. Poly-arginine (6–12 residues) also has the same transduction activity as the PTDs. PTDs have become widely used as tools for the delivery of proteins and various kinds of physiologically active substance in vitro and in vivo. We tried to apply this method for boron delivery in BNCT.

Today, two boron compounds, boronophenylalanine (BPA) and sodium borocaptate (BSH) are clinically used for BNCT. BPA, which transfers boron via L-type amino acid transporter, can deliver ¹⁰B even in the infiltrating tumor cell population where the BBB is intact. However, some amounts of ¹⁰B are inevitably taken into the normal cells by boronophenylalanine systemic administration. Moreover, the native heterogeneity of malignant gliomas interferes with the ability to accurately target the tumor. BPA is easily up-taken into highly proliferative cells that we call malignant cells, through the amino acid intake.

BPA localizes the tumor area and accumulates into brain tumor. On the other hands, BSH is transferred to brain tumors only through the disrupted blood-brain barrier (BBB), so it is difficult for BSH to reach regions that tumor cells invade microscopically where the BBB seems to be intact. On the other hand, recent reports have delineated boron delivery systems (Boron DDS) to improve molecular targeting of malignant gliomas. Peptide agents can be carried into brain tumor area after intravenous injection and easily leak from tumor vessel.

Results and discussions

The protein transduction system with cell membrane permeable peptide is useful system for delivering the various biological items from extracellular space to intracellular. The characteristic of cell membrane permeable peptide (CPP) is that CPP contains many basic amino acid like Lysine or Arginine. The Poly-Arginine is one of the best and the most powerful cell membrane permeable peptide for delivering biological compound into cell.

We made multi-BSH fused poly-arginine (1BSH-11R, 2BSH-11R, 4BSH-11R and 8BSH-11R) and one BSH fused short-arginine peptide (BSH-1R, BSH-2R, BSH-3R). Administration of multi-BSH-11R (8BSH-11R) showed tumor specific localization in mouse brain tumor model from mouse tail vein injection. But, at the point of drug synthesis, multi-BSH-11R was very difficult for making. On the other hand, BSH-3R is very easy to synthesis and high boron content in this molecule, and showed brain tumor specific localization in mouse brain tumor model.

These two types of BSH-CPP agents is useful for future application of clinical use for BNCT.

Conclusions

The new boron delivery system with tumor-specific-targeting and highly intracellular uptake is essential for BNCT. Peptide-Boron compound is good tool for boron drug delivery system (Boron DDS) in next generation BNCT.

References

- [1] Michiue H, Sakurai Y, Kondo N, Kitamatsu M, Bin F, Nakajima K, Hirota Y, Kawabata S, Nishiki T, Ohmori I, Tomizawa K, Miyatake S, Ono K, Matsui H., *Biomaterials*. 2014 Mar;35(10):3396-405
- [2] Hitsuda T, Michiue H, Kitamatsu M, Fujimura A, Wang F, Yamamoto T, Han XJ, Tazawa H, Uneda A, Ohmori I, Nishiki T, Tomizawa K, Matsui H., *Biomaterials*. 2012 Jun;33(18):4665-72.
- [3] Matsushita M, Tomizawa K, Moriwaki A, Li ST, Terada H, Matsui H., *J Neurosci*. 2001 Aug 15;21(16):6000-7

PS2 B 12

Preparation, Characterization and Evaluation of Boron-modified Diblock Copolymer as Vehicle for Boron Neutron Capture Therapy

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The development of boron-containing drugs, including boronic acid derivatives, sodium mercaptoundecahydro-closo-dodecaborate (BSH) and boronophenylalanine (BPA), aims to elaborate the clinical value of boron neutron capture therapy (BNCT). However, the delivery and accumulation of boron-containing drugs in tumor site are far from perfect. Integration of nanotechnology and BNCT may take advantage of accumulating boron-containing drugs in tumor through enhanced permeability and retention (EPR) effect. In the present work, biodegradable poly-D,L-lactide (PLA) capped with pinacol boronate ester (Bpin) was copolymerized with water-soluble polyelectrolyte poly(2-ethyl-2-oxazoline) (PEOz) to construct diblock copolymer, Bpin-PLA-PEOz, which could form polymeric micelles (BPP) in an aqueous solution. This boron-containing vehicle could be employed to encapsulate additional boron-payload, for instance phenylboric acid derivative (PBAD), to further multiply boron contents in Bpin-PLA-PEOz/PBAD polymeric micelles (BPPP). Hydrodynamic sizes are 162 nm and 152 nm for BPP and BPPP micelles, respectively, and values of zeta potential are around neutral. Also, BPP and BPPP micelles have shown high cell viability by MTT assay. We further inspect pharmacokinetics and biodisposition of BPP and BPPP micelles in rats and mice. The particle size, structural stability, water solubility, low cytotoxicity and evading renal filtration can be the proof-of-concept for polymeric micelles for BNCT. On the basis of these investigations, the BPP and/or BPPP micelles present a promising platform for treating tumor-bearing xenograft and lead to good tumor/plasma ratio for BNCT.

PS2 B 13

IN VITRO STUDIES OF CELLULAR RESPONSE TO DNA DAMAGE CAUSED BY BORON NEUTRON CAPTURE THERAPY (BNCT) IN A RECURRENT THYROID CARCINOMA

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Background

Some years ago, we started to study the effect of BNCT on DNA damage and the mechanisms of repair induced in a thyroid carcinoma. We observed different genotoxic patterns for tumor cells irradiated with gamma rays, neutrons alone and neutrons plus different boron compounds, boronophenylalanine (BPA) or α,β -dihydroxyethyl)-deutero-porphyrin IX (BOPP). In the present study we analyzed the damage profile of nuclear H2AX H2AX foci and the expression of Ku70 and Rad51, main components of non-homologous end joining (NHEJ) and homologous recombination repair (HRR) pathways, respectively, induced by BNCT in human cells of thyroid carcinoma.

Methods

Cells of the human follicular thyroid carcinoma line, WRO in exponential growth were distributed into the following groups: 1) Gamma irradiation, 2) irradiation with neutrons beam (N), 3) irradiation with neutrons plus BPA (BNCT). A control group for each treatment was included. The cells were irradiated in the thermal column facility of the RA-3 reactor (Flux= 1.10^{10} n/cm² sec) or with a ⁶⁰Co source. The irradiations were performed during different lapses of time in order to obtain a total physical absorbed dose of 3 Gy (\pm 10 %). The studies after irradiation were carried out after 30 minutes, 1, 2, 4, 6, 24 and 48 hours of incubation. DNA damage was evaluated by immunofluorescence using an anti-histone H2AX phosphorylation antibody indicating double strand break in the DNA. The protein expression of Ku70 and Rad51 was analyzed by Western Blot at different times post irradiation.

Results

The number of H2AX foci was higher in Gamma group after 30 minutes after the irradiation while the foci size was bigger in the BNCT group. The expression of Rad51 protein increased 4 hours after the irradiation and the levels remained high even after 48 hours in the N and BNCT groups ($p < 0.05$) while Ku70 did not show a significant change in its expression levels in all irradiated groups respect to the control group.

Conclusion

The larger H2AX foci size would indicate that the damage caused by BNCT is higher and more complex than that caused by gamma irradiation. The protein levels would indicate an activation of the HRR pathway in the thyroid carcinoma cells treated by BNCT. Ku70 genetic expression was not modified suggesting a post-translational effect either or protein degradation. These findings are consistent with the mRNA levels of the respective proteins determined previously. The knowledge of repair mechanisms will allow us to manipulate the tumor response to the irradiation in order to increase the efficacy of the therapy.

PS2 B 14

Preliminary in vivo studies for the application of Boron Neutron Capture Therapy (BNCT) to the treatment of differentiated and recurrent thyroid carcinoma using the histone deacetylase inhibitor, sodium butyrate (NaB) as a radiosensitizer.

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Abstract: Background

The sodium butyrate NaB is a short chain fatty acid that belongs to a group of

compounds described as histone deacetylases inhibitors (HDACI). Previously we have performed studies using NaB in combination with boron neutron capture therapy (BNCT) for the treatment of thyroid carcinoma. We demonstrated *in vitro* that the addition of NaB to the administration of boronophenylalanine (BPA) in the cell culture prior to the irradiation with neutrons produced: decrease of cell survival and increase the percentage of apoptotic and necrotic cells. Besides, *in vivo* we observed that when we administrated NaB one day previous to the BPA, boron uptake selectively increased in the tumor. The aim of this work was to investigate if NaB besides increasing the boron concentration also has a radiosensitizer effect in the neutron capture reaction in the tumor.

Methods

NIH nude mice (50 individuals) of 6-8 weeks of age were injected subcutaneously in the back right flank with 1.5×10^6 human follicular thyroid carcinoma (WRO) cells. Twenty days after, tumor bearing animals (tumor size $< 50 \text{ mm}^3$) were irradiated at the RA 6 reactor (Flux: $4.75 \cdot 10^8 \text{ n/cm}^2 \cdot \text{s}$) at Centro Atómico Bariloche (CAB). The experimental groups were: 1) Neutrons (N, irradiated with neutron beam, without BPA), 2) Neutrons + Sodium Butyrate (N + NaB), 3) Neutrons + BPA (BNCT), 4) BNCT + sodium butyrate (BNCT+NaB), 5) Control: no irradiation, no compounds. The evolution of the animals was followed during 31 days by tumoral growth.

Results

Ten days after the treatments, all tumors irradiated decreased their volume while control tumors kept growing. After that time, tumors started to grow again only in animals of groups 1 and 2. A complete remission of tumor was observed in the 30 % of the animals of groups 1 and 2, 75 % in group 3 and 70 % in group 4, during the follow up period (31 days). In the BNCT groups, with or without NaB approximately the 80 % of the animals remained free of tumors. The total physical absorbed doses were: 2.92 Gy for groups 1 and 2, 4.73 Gy for group 3 and 5.11 Gy for group 4.

Conclusion

These preliminary results showed no significant differences between groups that received NaB and those that did not. Further studies with tumors of different sizes are needed to determine the efficacy of NaB in the improvement of BNCT for the treatment of thyroid carcinoma.

PS2 BI 01

New approach to real-time measurement of the number of $^{10}\text{B}(n, \alpha)^7\text{Li}$ reactions using Gaseous Electron-Tracking Compton Camera (ETCC) system in boron neutron capture therapy

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Introduction

In boron neutron capture therapy (BNCT), dose with high LET by $^{10}\text{B}(n, \alpha)^7\text{Li}$ reaction is deposited in tumors. Transition probability of 478 keV gamma-ray emitted from $^7\text{Li}^*$ excited state in the $^{10}\text{B}(n, \alpha)^7\text{Li}$ is 93.7 %. This study is a feasibility test for evaluating the number of $^{10}\text{B}(n, \alpha)^7\text{Li}$ reactions by counting the 478 keV gamma-rays emitted from the region of interest with a Compton camera system.

Materials and Methods

Our institution has been installing an accelerator-based BNCT system. In order to evaluate the number of the neutron capture reactions, we are going to use a Gaseous Electron-Tracking Compton Camera (ETCC) system which consists of a gaseous chamber and a GSO scintillator array. Although commonly Compton camera systems determine emission angles of gamma-rays by measuring position and energy of recoil electron and energy of scattered gamma-rays by a semiconductor detector, the ETCC provides direction of recoil electrons in addition by the gaseous tracker. Therefore, energy, direction and position of initial gamma-ray are determined with high precision. Moreover, the background gamma-rays which have much lower energies than 478 keV can be effectively eliminated using the ETCC. Imaging of ^{198}Au and ^{18}F which were measured with the ETCC system succeeded. The modeling of the BNCT system in our institute was performed with a Monte Carlo simulation package, Particle and Heavy Ion Transport code System (PHITS, version 2.64). Simulations with the PHITS are performed for estimation of an energy spectrum of the initial gamma-rays emitted by irradiation of ~ 800 keV neutron to a water phantom of $30 \times 30 \times 20$ cm³. Beam aperture is placed on top of the water phantom. The central axis of the water phantom corresponds to the beam central axis. To simulate the tumor region with high concentration of ^{10}B , ^{10}B was placed in the restricted region of $3 \times 3 \times 3$ cm³ in the water phantom. ^{10}B density used were 25 ppm, 250 ppm, and 2 500 ppm. For these simulations, the number of neutrons was always 6.3×10^7 . The energy distribution of the neutrons was evaluated with another independent simulation. The initial gamma-rays are counted at a distance of 12 cm from the tumor region after penetrating the sensitive area. In this study, the number of 478 keV gamma-rays was extracted by interesting the counts of gamma-rays whose energies lie between 460 keV and 480 keV.

Results

The number of 478 keV gamma-rays is almost proportional to the density of the ^{10}B . When the density of the ^{10}B is 250 ppm, the number of the measured gamma-rays between 400 keV and 2.5 MeV is $1.1 \times 10^{11}/\text{s}$, and that of the 478 keV gamma-rays is $2.9 \times 10^9/\text{s}$.

Discussion

The ETCC system can sustain a data acquisition rate of a few kcps. If the distance between the tumor and the detector is 300 cm, the number of the 478 keV gamma-ray rate is $6.2 \times 10^6/\text{s}$. Therefore, with using the shield material, this study showed that the ETCC system would be applicable to BNCT. In the future, we investigate the detection efficiency of the ETCC system.

PS2 BI 02

Autoradiography for cell culture testing: Preliminary Results

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Introduction

The autoradiography techniques using solid state nuclear track detectors (SSNTD) are often used and well established for the quantitative analysis of B¹⁰ distribution in tissue or blood. On the other hand the B¹⁰ amount in cell culture samples can be measured via inductively coupled plasma mass spectrometry.

In order to establish an alternative boron measurement technique for cell culture samples we start combining both techniques to evaluate the possibility of using autoradiography for a more detailed and easier analysis of boron amounts in cell samples.

Materials and Methods

Cells from established cell lines were grown in 6-well plates and contemporaneous in petri dishes and are treated with B¹⁰ enriched BPA (Katcham). After trypsination the smaller cell-pellets were used for cytopspins, which are irradiated in the TRIGA Mark II research reactor of the University of Mainz for preparation of the autoradiographic images. The films were irradiated at a flux of $2.3 \cdot 10^5$ n/cm²·s for 20 minutes in the thermal column of the reactor. The pellets from the petri dishes were analyzed via inductively coupled plasma mass spectrometry.

Results

The proportions of the results via inductively coupled plasma mass spectrometry could be seen in the data of the autoradiography. There is a strong dependency between the centrifuged cell number and the statistical uncertainties of the results.

Conclusion

It is possible to use the autoradiography to measure the boron content of cell samples. A quantification of the results is only possible by analyzing identical samples via inductively coupled plasma mass spectrometry.

PS2 BI 03

Application of micro-PIXE/PIGE technology to boron concentration analysis

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[Introduction] We already reported the boron imaging using micro-PIXE/PIGE system. Micro particle induced X-ray emission (micro-PIXE) and particle induced gamma ray emission (PIGE) were applied to determine the intratumoral distribution of ¹⁰B atom in tumor cells or tissue (K. Endo et al, Y. Yamamoto et al). Under the accelerator based NCT, we need to develop a new methods that take the place of PGA boron analysis with reactor based NCT. We investigated the

possibility of application to boron analysis during clinical irradiation.

[Material and Methods] Various concentration of boron solution were dripped and dried on the thin polycarbonate membrane, which glue on the aluminum sample folder. The samples were irradiated with a 1.7MeV proton beam collimated to a 1 μ m diameter and the emitted gamma-rays were detected. U251 and CT26 cell lines were cultured on the polycarbonate membrane. These cells were treated with 0, 38, 300 μ g/ml of f-BPA for 2 hours, with or without PBS wash, fixed with acute freeze-drying. The samples were analyzed to detect the boron using the micro-PIXE analysis system with a 15 to 60 minute measuring time.

[Results and Discussion] Boron peak from 1 μ l of 18 μ gB/ml BPA solution was detectable from in-air measurement. At this time, to evaluate the clinical sample during irradiation, more quick and accurate analysis system is required. 2hours of f-BPA exposure make a boron existing image by PIGE, but PBS wash group cannot detect the boron. It means that under the 2hours f-BPA exposure, boron atoms existing on the surface of cell membrane.

PS2 P 01

Mock-up Experiment at Birmingham University for BNCT Project of Osaka University - Neutron Flux Measurement with Gold Foil

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In Osaka University development of a new accelerator-based neutron source (ABNS) for BNCT is now in progress under the collaboration with Sumitomo Corporation and Mitsubishi Heavy Industries Mechatronics Systems, Ltd. The ABNS employs an electrostatic accelerator which produces low energy neutrons of $\sim 10^{13}$ n/sec having several hundreds keV via p-Li (${}^7\text{Li}(p,n){}^7\text{Be}$) reaction. By this neutron source, exposure dose of patients could be suppressed substantially. In the present paper, neutron flux measurement with a moderator/collimator mock-up of the new ABNS was carried out at Birmingham University, UK, to make sure of the accuracy of the design tool especially from the viewpoint of neutron flux intensity.

In this experiment, we measured spatial distributions of neutron flux intensity indirectly by the foil activation method with gold foil. At first, we positioned gold foils at various places under and inside the moderator/collimator assembly. Neutrons were thereafter irradiated to activate gold atoms by neutron capture reaction. After that, gamma-rays emitted from the gold foils were measured to evaluate the number of activation, i.e., reaction rate. Finally, we evaluated the spatial distribution of neutron flux intensity indirectly from the measured reaction rate and compared with calculated results by MCNP-5.

From the measurement, it was found that the reaction rate just under the assembly changed drastically as 100 %, 38 %, 5.7 % and 0.73 % for radial positions of $r = 0$ cm, 10 cm, 20 cm and 40 cm from the center, respectively. It shows that the neutron beam was well collimated within 10 cm in radius, while the collimator radius is 10 cm. By comparing this experimental result with simulation result calculated by MCNP-5, we confirmed a good agreement between them; the difference was roughly less than 10 % for 62 foils used. Remarkably, just under the assembly, the ratio between calculated and experimental result was 1.01 ± 0.01 .

In conclusion it was confirmed that our moderator/collimator assembly had an excellent collimation performance of neutron beam. The good agreement between experiment and simulation shows validity of other predicted design values calculated with MCNP-5, such as neutron spectrum, absolute flux intensity and so on. It was thus experimentally proved that upcoming design of our new ABNS would be quite reliable.

PS2 P 02

Design of A New Wide-dynamic-range Neutron Spectrometer for BNCT with Liquid Moderator and Absorber

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Boron Neutron Capture Therapy (BNCT) is a new treatment for cancer. Cases are reported only using nuclear reactors now. Recently, instead of nuclear reactor, accelerator based neutron sources (ABNS) are being developed for BNCT. However, their intensities are still weak, and patients should be hence positioned near the target. It causes difficulty to moderate neutrons sufficiently. As a result, the neutron energy spectrum is distorted depending on accelerators because high-energy neutron ratio changes depending on type of the accelerators. Therefore we must know each energy spectrum for each ABNS, especially in epithermal region. In the present paper, we carried out a new design study to measure neutron energy spectrum in thermal (< 0.5 eV), epithermal (0.5 eV ~ 10 keV) and high energy region (> 10 keV) more accurately and precisely with a Bonner type spectrometer.

Neutron detector's response for specified energy neutron can vary by covering the neutron detection device with moderators or absorbers. We can estimate the neutron energy spectrum by unfolding a set of count rates obtained by detector for each parameter of the moderators and absorbers, i.e. material, thickness, density and so on. Generally, in this method, the more the number of detector's response functions is, the better the accuracy and precision of inferred energy spectrum are. In the present study, we aim to increase the number of response functions dramatically by using liquid materials by which we can adjust their thickness continuously. For this purpose, we carried out numerical tests to confirm the ability of this method to reproduce the true energy spectra from experimental results. At first, the response functions were evaluated by A General Monte Carlo N-Particle Transport Code, Version 5 (MCNP-5). For a neutron detection device, a ^3He proportional counter was assumed. Water, hexane and boric acid aqueous solution were considered as moderators and absorbers. After that, count rates were calculated by folding process with the

evaluated response functions and assumed neutron energy spectra. To simulate measurement, statistical errors were added to the count rates. In the analysis the neutron spectra are assumed to be Maxwellian distributions having peaks at every decade between 0.01 eV and 10 MeV. Finally we estimated the neutron energy spectra by unfolding the count rates with additional errors and confirmed the reproducibility comparing with the true (assumed) spectra. For unfolding, we used Bayesian estimation method to evaluate without “initial guess spectrum” and as a result physically meaningless minus spectrum can be avoided.

From the result of numerical tests, we confirmed spectrum reproducibility of the method for energy range between 0.1 eV and 1 MeV with high accuracy and precision for cases with boric acid in less than 5 % error and with water and hexane in less than 2 % error.

In conclusion, we confirmed the prospect of a new approach to measure the neutron energy spectrum in a very wide dynamic range, including epithermal neutrons which are indispensable for BNCT, by using liquid moderators and absorbers. In future, we will develop a proto type of the presently proposed detector and examine the validity of the method experimentally.

PS2 P 03

Mock-up Experiment at Birmingham University for BNCT Project of Osaka University - Gamma-ray Dose Measurement with Glass Dosimeter

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In Osaka University, a new neutron source project based on an accelerator and lithium target is under preparation for BNCT. In the system, an electrostatic accelerator and a liquid Li target are employed to suppress the exposure dose of patients. On 2013 mock-up experiments with a moderator/collimator assembly were performed at Birmingham University under the support of Sumitomo Corporation and Mitsubishi Heavy Industries Mechatronics Systems, Ltd. In the present paper, spatial distributions of gamma-ray dose under the moderator/collimator assembly are reported, and evaluation of gamma-ray dose in the mixture field with neutron and gamma-ray are discussed.

In the experiment, a lot of glass dosimeters were placed on various places, inside and outside of a human body phantom, to measure spatial distributions of gamma-ray dose. The glass dosimeter can measure gamma-ray dose from the radio photoluminescence, i.e., fluorescence is emitted from the glass compound as luminescent material by irradiation of ultraviolet light. The fluorescence varies in proportion to the amount of deposited energy of radiation. The shape of the glass dosimeters employed here was a cylinder with 1 mm in diameter and

15 mm in length. The spatial distribution of gamma-ray dose was estimated indirectly from the measured values of the glass dosimeters and compared with calculated results by MCNP-5.

From the neutron flux measurement in the series Birmingham experiments, it was found that neutron flux was well collimated within 10 cm radius, whereas our collimator radius was 10 cm. As for gamma-ray in this study, similar to the neutron flux, the gamma-ray doses just on-axis of the assembly has high intensity within the collimator radius and drastically decrease with a distance from the axis. The measured gamma-ray doses were found to be higher than the simulation result from MCNP-5. The reason is that the glass dosimeters are excited by neutrons in addition to gamma rays, because radiation field in BNCT is the neutron/gamma-ray mixture field. In this study, a method using a lead filter was thus utilized and discussed for an accurate evaluation of gamma-ray doses in the mixture field. The method could indicate more accurate gamma-ray doses by making a difference of doses measured with a pair of glass dosimeters, i.e., with and without the lead filters placed on the same position. Obtained results from these experiments are presented and discussed.

PS2 P 04

Neutron Intensity Monitor with Activation Foil for p-Li Neutron Source for BNCT

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Proton-lithium (p-Li) reaction is being examined as a candidate nuclear production reaction for accelerator based neutron source (ABNS) for BNCT. With proton energy of around 2.5 MeV, the produced neutron energy can be controlled to be sufficiently low in order to suppress secondary gamma-rays. Several research groups are now developing a new ABNS with this reaction for BNCT.

It is well known that the number of neutrons produced by p-Li reaction can be confirmed by measuring radioactivity of the target after irradiation by means of gamma-ray spectrometry. However, in an actual BNCT, it is not so easy to perform the process because it is not easy to remove the target after irradiation. In the present study, was investigated how to monitor the absolute neutron intensity of the p-Li neutron source easily.

For a simple measurement in the real BNCT scene, we are examining activation foils suitable for measuring neutrons produced by p-Li reaction, which are around several hundreds keV. This kind of foil is not known so far. In the present study, the feasibility was discussed by checking all the reactions of stable nuclides induced by neutrons. Of course, for thermal and fast neutrons there are a lot of activation foils known to be available. However, for keV region neutrons it is quite difficult to apply activation foil method. From the result of examination, there are some possibilities in isomer production reaction via inelastic scattering.

Practically, nuclear reactions having low threshold energies of up to around several hundreds keV were examined by calculating their reaction rates taking into consideration their activation cross sections and the emission angle-dependent spectrum of neutrons emitted via p-Li reaction. As a result, it was

found that ¹¹⁵In, ¹⁰⁷Ag, and ¹⁸⁹Os would be feasible. Their features found out are summarized as in the following:

¹¹⁵In: Cannot be used for backward emission angles. However, the accuracy is the best at 0 deg.

¹⁸⁹Os: Only nuclide which can be used in backward angles. However, the gamma-ray energy is a little too low.

¹⁰⁷Ag: The most convenient foil, since the half life is short.

In the next step, validity of these foils will be examined experimentally using a p-Li neutron source.

PS2 P 05

Potential application of NIPAM polymer gel for dosimetric purposes in BNCT

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Boron neutron capture therapy (BNCT) is based on selective accumulation of ¹⁰B inside the tumor cells with subsequent irradiation of tumor using neutron beam. In general, total dose from BNCT can be attributed to four components: the gamma dose, epithermal and fast neutrons dose, the dose from thermal neutron captured in ¹⁴N and the dose from thermal neutron captured in ¹⁰B. Since the dose components have different relative biological effectiveness (RBE), the dose distribution measurement in different normal and tumor tissues is very important. To determine the total dose delivered to the patient and to predict the therapeutic effectiveness of BNCT, the dose components must be measured by particular dosimetry procedure. The principal method recommended for determining fast and epithermal neutron and photon dose is dual ionization chamber technique. The dose contribution from thermal neutron captured in nitrogen-14 and boron-10 is calculated from the measured thermal neutron flux. Although these methods are commonly used in clinical dosimetry of BNCT, they have some disadvantages such as: 1) dosimetric process is very *time-consuming*. 2) The thermal neutron doses are not measured directly. 3) require two different dosimetric methods to detect various radiation types and total dose calculation. 4) Ionization chambers need several correction factors. To overcome these limitations, a more efficient and reliable dosimeter is needed. Since the polymer gel dosimeters are normally tissue equivalent and are able to record dose information in three-dimensions with sufficient spatial accuracy, therefore could be a suitable option for dosimetric purposes in BNCT. The study is currently in progress to explore the applicability of NIPAM gel in BNCT.

PS2 P 06

Problems of neutron spectrum measurements with TOF technique and their solutions

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At BINP it is constructed and launched the tandem accelerator with vacuum insulation for BNCT. Results achieved in long stable generation of neutrons at 1 mA proton beam allowed us to measure neutron spectrum using time-of-flight (TOF) technique. To create short neutron pulses it is applied a new technical solution, which is briefly described below. Accelerator operates in a stationary mode, generating protons with energy 1.875 MeV, just below the neutron production threshold. Protons with subthreshold energy hit the electrically insulated lithium target, which at the same time is supplied with negative short (200 ns) square pulses having amplitude 40 kV and frequency 100 Hz. During each high voltage pulse the energy of protons increases up to 1.915 MeV and neutrons are generated. The energy of emitted neutrons is calculated after measuring the time gap between high-voltage pulse and neutron pulse in the remote neutron detector. Previously this method of generating short neutron pulses nobody applied, so we had to solve a number of unexpected problems that prohibit carrying out spectrum measurements. An interesting problem was the noise signal on the resulting neutron spectrum. It was discovered several sources of noise, namely: 1) scattered neutrons; 2) neutrons generated in the reactions $^{55}\text{Mn}(p,n)^{55}\text{Fe}$ and $^{63}\text{Cu}(\alpha,n)^{66}\text{Ga}$ (α -particles from $^7\text{Li}(p,\alpha)\alpha$ reaction), caused by proton beam interaction with construction materials; 3) high intensity γ -ray flow; 4) insufficient stability of the proton energy leading to unwanted neutron generation when the threshold 1.882 MeV is exceeded. Original technical solutions to suppress this noise and a special method of controlling signal-to-noise ratio are described in detail in this article. As a result of applying these solutions we were able to measure neutron spectrum using TOF at proton energy 1.915 ± 0.005 MeV. The resulting neutron spectrum compared with MCNP calculation is also presented in this work.

PS2 P 07

n_TOF (CERN) planning experiments to improve BNCT dosimetry: $^{35}\text{Cl}(n,p)$ and $^{14}\text{N}(n,p)$ cross section measurements.

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For BNCT treatments, dose delivery in tissue is obtained by means of kerma-fluence factors where the most important isotopes including in these calculations are ^1H , ^{12}C , ^{14}N , ^{16}O and ^{10}B . Furthermore, ^{35}Cl is also important for brain tumors since chlorine is present in higher concentration in brain than in the rest of the human body. The accuracy of the results strongly depends on the evaluated nuclear data included in the calculations. In order to improve the nuclear data available in the epithermal neutron energy range, a set of new cross-section measurements are planned to be performed at n_TOF, the spallation neutron time-of-flight facility at CERN consisting of two experimental areas (EAR). EAR-1 is located underground at 185 m from the spallation target in the direction of the incoming proton beam. In the last ten years it has been used for measuring neutron-capture and neutron-induced fission cross-sections of interest in

nuclear technologies and astrophysics with very high energy resolution. A new experimental area (EAR-2, to be ready in 2014) will be located above the ground at 20 m from the spallation target in the perpendicular direction of the incoming proton beam. The main advantage of EAR-2 is that the expected neutron flux will be increased by a factor of 25 in comparison with EAR-1, thus a higher neutron rate which will allow the use of smaller samples. This is very important for reducing the activity of radioactive samples or the possibility of using small samples of rare materials. Measurements can be also performed on isotopes with small cross-sections, as the case of $^{14}\text{N}(n,p)^{14}\text{C}$, of importance in BNCT. However, the capability to resolve resonances in the keV-MeV range is higher in EAR-1. In November 2012, we carried out the measurement of the cross-section of the $^{35}\text{S}(n,\alpha)^{30}\text{Si}$ reaction with MicroMegas detectors at n_TOF-EAR1 trying to clarify the discrepancies between the resonance parameters of the sole (n, α) measurement and the sole transmission measurement. The $^{35}\text{S}(n,\alpha)^{30}\text{Si}$ is of interest due to its potential use as cooperative target in BNCT. In 2015, it will be performed the $^{35}\text{Cl}(n,p)^{35}\text{S}$ and the $^{14}\text{N}(n,p)^{14}\text{C}$ cross-section measurement at n_TOF-EAR1 and n_TOF-EAR2, respectively. In the case of $^{35}\text{Cl}(n,p)$, there is only one differential measurement that covers partially the energy range of interest in NCT. Concerning $^{14}\text{N}(n,p)^{14}\text{C}$, there are three different measurements performed in three different setups cover the NCT energy range. The experimental set-up prepared for the latest two measurements at n_TOF would be similar to that used for ^{35}S . Nevertheless, the background level for MicroMegas detectors is in the energy range of the emitted protons, therefore Silicon Monitor detectors (SiMon) would be also studied. The aim of this work is to show the possibility of improving the BNCT dosimetry for epithermal neutron beams by means of new experimental measurements at n_TOF (CERN) which would increase the accuracy of the existing experimental data needed to calculate the kerma-fluence factors. Furthermore, Monte Carlo simulations of the deposited dose in a ICRU 4-component material (H, C, N and O), with and without the presence of ^{35}Cl , as well as the comparison between different evaluated data will be presented in order to support this work.

PS2 P 09

Design of epithermal and thermal neutron beams for accelerator based BNCT applying to the TRIGA-II research reactor facility - (1) Cyclotron accelerator (proton energy 30MeV and electric current 1mA)

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Introduction

A research reactor has been used for BNCT treatment because of sufficient neutron flux and long term working stability. However accelerator based BNCT is now attractive for hospital based conventional radiotherapy due to advance of the accelerator technology resulting in development of a small accelerator. In this study, we have designed thermal and epithermal neutron beams applicable to BNCT in order to install the cyclotron accelerator into the Musashi Institute of Technology Research Reactor (MITRR, TRIGA- II) facility.

Materials and Methods

We use the cyclotron accelerator (proton beam 30 MeV and accelerator current 1mA) of Sumitomo Heavy Industries (SHI) which has been used in Kyoto University Research Reactor Institute (KURRI) aiming at development of the cancer treatment system by BNCT. The beryllium target producing neutrons by

(p,n) reactions is selected which puts at the center of the reactor core of MITRR. The proton beam injects into the beryllium through one of the horizontal experiment hole. We have designed both thermal and epithermal neutron beams at thermal and thermalizing columns respectively, by investigating several materials to get optimal arrangement of moderator, neutron filter, gamma-ray shielding and neutron collimator. A particle and heavy ion transport code system (PHITS) was used for the calculation with statistic error of less 8 %.

Result

We calculated neutron and gamma-ray spectra as well as fluxes at the thermal and epithermal neutron irradiation fields. The calculation results are as follows: In the thermal column, (1) thermal neutron flux is $1.8E+09$ [n/cm²/sec]. (2) fast neutron dose component is $3.3E-17$ [Gy · cm²/n]. (3) gamma-ray dose component is $1.1E-13$ [Gy · cm²/n]. In the thermalizing column, (1) epithermal neutron flux is $1.0E+09$ [n/cm²/sec]. (2) fast neutron dose component is $3.1E-14$ [Gy · cm²/n]. (3) gamma-ray dose component is $4.0E-14$ [Gy · cm²/n].

These results were satisfied with design values. Therefore, we believe that these beams can be applied to BNCT treatment.

Conclusion

Enough thermal and epithermal neutron fluxes were obtained at the thermal and thermalizing columns, respectively, and extra dose components mixing in the beams were satisfactory. An accelerator based BNCT could be possible if such beams would be designed by setting up the cyclotron accelerator (proton beam 30MeV and accelerator current 1mA) at the TRIGA-II research reactor facility under decommissioning.

PS2 P 10

Design of epithermal and thermal neutron beams for accelerator based BNCT applying to the TRIGA-II research reactor facility (2) Linac accelerator (proton energy 8MeV and electric current 10mA)

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Introduction

1.25 million Japanese people were died in 2011 and one third of death was due to cancer. Boron Neutron Capture Therapy (BNCT) is one of radiation therapy effecting cellular-level in tumors. So far, BNCT has been only performed by research reactors. However, regulation requires long shut-down for maintenance. An accelerator is recently developed as a neutron source by technical improvement. Some accelerator based BNCT facility is now under construction following Kyoto University Research Reactor Institute (KURRI) in Japan. In this study we investigate a linac accelerator into the Musashi Institute of Technology Reactor (MuITR, TRIGA-II 100kW) and design thermal and epithermal neutron beams for accelerator based BNCT applying to the research reactor facility under decommissioning.

Materials and Method

We used the linac accelerator (proton energy 8MeV and electric current 10mA). A

⁹Be target was selected as the neutron production material. We designed thermal neutron and epithermal neutron beams at the thermal and thermalizing columns respectively where the ⁹Be target was put at the center of core. A proton beam irradiated at the ⁹Be target through one of horizontal experimental holes. We examined several materials and shapes of a moderator/ filter /gamma-ray shield in order to satisfy the design goal. Calculation was carried out by using Particle and Heavy Ion Transport code System (PHITS) with statistical error of less 8 %.

Result

We have calculated neutron and gamma-ray spectra as well as both fluxes in the thermal and epithermal irradiation fields.

The results were as follows: In the thermal neutron irradiation field,

- (1) Thermal neutron flux $\Phi_{th} = 1.0 \times 10^9$ (n/cm²/s).
- (2) Fast neutron dose component $D_{fast}/\Phi_{th} =$ less than design value of 5.0×10^{-13} (Gy \cdot cm²).
- (3) Gamma-ray dose component $D_{\gamma}/\Phi_{th} = 4.7 \times 10^{-13}$ (Gy \cdot cm²).

In the epithermal neutron field,

- (1) Epithermal neutron flux $\Phi_{epi} = 1.2 \times 10^9$ (n/cm²/s).
- (2) Fast neutron dose component $D_{fast}/\Phi_{epi} = 2.4 \times 10^{-12}$ (Gy \cdot cm²).
- (3) Gamma-ray dose component $D_{\gamma}/\Phi_{epi} = 4.7 \times 10^{-13}$ (Gy \cdot cm²).

Conclusion

Enough thermal and epithermal neutron fluxes were obtained at the thermal and epithermal irradiation fields, respectively, but fast neutron dose component in the epithermal neutron beam was higher than design value. Further examination is necessary for design of the epithermal neutron beam and also heat removal of ⁹Be target with the cooling system.

PS2 P 11

Feasibility study of using laser accelerator to produce appropriate neutron beam for BNCT: MCNP Simulation

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Laser-driven ion acceleration and its applications are now actively studied all over the world. Some experiments are done to produce neutron source by laser-accelerated protons. The aim of this work is the feasibility study of using laser-accelerated proton beam to provide a neutron source for BNCT application. The proton energy spectrum accelerated on the VULCAN laser was measured and analyzed. The measured proton spectrum was found to exhibit a broad Boltzmann-like distribution with a temperature of 5 MeV. The maximum detected proton energy was 42 MeV and the total number of protons accelerated to energies above 10 MeV was approximately 5×10^{11} . We have used the mentioned proton spectrum to produce neutrons using (p,n) reaction and an appropriate target material. Different thicknesses of some target materials including ^{nat}Pb, ^{nat}Cu, ⁶⁶Zn, ⁶⁷Zn, ⁶⁸Zn, ^{nat}W, ⁷Li, ⁶Li, and ⁹Be have been tested to produce appropriate neutron beam. The target optimization has been performed to produce more neutron N_{nr} with the lowest mean neutron energy, E_n (which

must be moderate to epithermal energy), to obtain the maximum value of Figure of Merit, $FOM = N_p / E_n$. According to the results, ^{68}Zn with 5 mm thickness has been selected as the optimized target. In the next step, a Beam Shaping Assembly (BSA) has been designed based on the produced neutron beam specifications. The final designed beam provides $\sim 10^5$ (n/cm²) epithermal neutron which is not sufficient for BNCT treatment, but this neutron beam can be used for biological researches, in-phantom dosimetry, animal treatment, etc. To provide appropriate epithermal neutron flux for BNCT treatment, the laser must operate at repetition rates of 10 kHz, which is rather ambitious at this moment.

PS2 P 12

Investigation on the reflector/moderator geometry and its effect on the neutron beam performance in BNCT

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In order to provide an appropriate neutron beam for Boron Neutron Capture Therapy (BNCT), an especial Beam Shaping Assembly (BSA) must be designed based on the neutron source specifications. A typical BSA includes moderator, reflector, collimator, thermal neutron filter, and gamma filter. In common BSA, the reflector is considered as a single layer covering the moderator materials. In this paper, new reflector/moderator geometries including multi-layer and hexagonal lattice have been suggested and their effect have been investigated by MCNP4C Monte Carlo code. In the multi-layer configuration, annular reflectors are considered in three layers which covered moderator layers. Eight cases have been evaluated based on the material in each reflector layer. In the hexagonal lattice geometry, rod reflectors with different radius have been arranged in the moderator material in different lattice pitches. In each case, neutron beam parameters have been calculated by MCNP Monte Carlo code. The results show that epithermal to thermal neutron flux ratio corresponding to the suggested configurations is significantly larger than its value in common configurations. This is an important advantage for these configurations because they do not require any thermal neutron filters which in almost cases, cause to increase the gamma contamination in the neutron beam due to (n,γ) interaction by the filter materials. The results also show that there is no preference in epithermal neutron flux point of view between suggested and common configurations. So, the neutron beam performance corresponding to the suggested configurations is better than common suggested configuration.

PS2 P 13

Design of Photon Converter and Photoneutron Target for High Power Electron Accelerator Based BNCT

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At recent years linear accelerators (Linacs) have been considered as a favorable facility for BNCT application due to compactness, easy handling, adjustable flux, no radioactive waste, and less shielding requirements. Although photoneutron production isn't an efficient way to produce enough neutron for BNCT, but it would be possible using linac with high average beam current. ILU-14, the industrial and powerful electron accelerator, can produce 10 MeV electrons in average current of 10 mA. Melting down may be cause due to impinging of such focusing beam on photon target because the temperature of target will be increased more than melting point even in first moments of irradiation. A solutions proposed in this work are using of scanning beam instead of focusing beam and designing a heat removal system. At first step with focusing beam, targets with disc and cylindrical geometry have been designed for photon converter and photoneutron target, and according to the scanning beam, their dimensions and geometries have been changed.

Different materials in various geometries with reasonable size, cost and availability have been studied for an optimized neutron target for ILU-14 in order to use for BNCT. All optimization calculations for targets have been performed by Monte Carlo MCNPX2.6 code.

According to the results, tungsten strip with 54 cm in length, 2 cm in width, and 0.15 cm in thickness has been introduced as the photon target, and D₂O in cylindrical form with 26 cm in radius and 16 cm in thickness has been selected as the photoneutron target. A water cooling system has been proposed to reduce the temperature of the target (around 14 C). Heat transfer evaluations in neutron target (consist of photon and photoneutron targets) have been performed by ANSYS software. The results show that this combined target can produce epithermal neutron flux about 1.24×10^8 (n.s⁻¹.cm⁻²) at therapeutic window which can be appropriate for BNCT.

PS2 P 14

Modification of the argon stripping target of the tandem accelerator

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For development of the accelerating concept of neutron capture therapy, the tandem accelerator with vacuum insulation is proposed and developed. In the tandem accelerator negative hydrogen ions are accelerated by the positive potential of the high-voltage electrode, converted into protons in the stripping target inside the electrode, and then protons are accelerated again by the same potential. Stripping target is made as a tube 16 mm in diameter and 400 mm long with the supply of the stripping gas (argon) in the middle. When studying the dependence of beam stripping on the argon pressure we have found an effect that can be explained by the appearance of the additional flow of positively charged ions of the stripping gas in accelerating channels. The interaction of the injected ion beam with the gas in the stripping target leads to ionization of the argon and to appearance of a low-ionized plasma with a positive potential. Under the influence of this potential part of positive argon ions comes out of the stripping target, enters into the acceleration channel where it is accelerated. This effect causes an additional load of power source, deterioration of the high-voltage

strength in the vacuum gap and limiting of the proton beam current. Suppression of the ion flux of the stripping gas is proposed using a transverse magnetic field applied in the region between the stripping target and the apertures in the high-voltage electrode. The paper presents the results of measurements of the ion beam current at the output of the accelerator depending on the argon pressure. Also the scanning electron microscope observations of the diaphragm surface modified by accelerated argon ions, and the results of direct measurements of the specially installed argon ion current detector are presented. The paper presents and discusses the project of modified gas stripping target. The idea of the target modification is the following. Inside the high-voltage electrode just behind inlet aperture it is proposed to apply 1 T transverse magnetic field using two-pole permanent magnets. In this field a parallel shift of the injected beam of negative hydrogen ions is performed. Similar magnets at the exit of the stripping target return proton beam back to the axis of accelerator channel. In this geometry not only significant suppression of ion penetration of the stripping gas into the accelerating channel can be achieved, but also a significant improvement of vacuum conditions in the accelerating channel and reduction of the ultraviolet radiation from the plasma in the stripping target. It is enough to shift the stripping target to a distance greater than the aperture (20 mm) in the high-voltage electrode and to implement a differential gas pumping. The paper presents results of trajectory calculation of the injected ion beam, evaluation of its emittance increase because of the magnetic field penetration into the stripping tube and selection of the optimal solution. The geometry of the magnetic system and the system of differential gas pumping using turbomolecular pump installed inside the high-voltage electrode are presented. The work plan for the stripping target modification and increasing the proton beam current is discussed.

PS2 P 15

A new concept of a Vacuum Insulation Tandem Accelerator

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Tandem accelerator with vacuum insulation has been proposed and developed in Budker Institute of Nuclear Physics. Negative hydrogen ions are accelerated by the positive 1 MV potential of the high-voltage electrode, converted into protons in the gas stripping target inside the electrode, and then protons are accelerated again by the same potential. Potential for high voltage and intermediate electrodes are supplied from the sectioned rectifier of electron accelerator ELV produced by the Institute for a long time, through sectioned feedthrough insulator with a resistive divider. In this work, we propose a radical improvement of the accelerator concept. It is proposed to abandon the separate placement of the accelerator and the power supply and connecting them through the feedthrough insulator. It is proposed to locate the source of high voltage inside the accelerator insulator, high voltage and intermediate electrodes mounted on it. This will reduce the facility height from 7 to 3 m and make it really compact and attractive for placing in a clinic. This will also significantly increase the stability of the accelerator, because the potential for intermediate electrodes can be fed directly from the relevant sections of the rectifier. The paper presents and discusses technical solution for making compact sectioned rectifier, scheme of its placement inside the insulator, and the benefits of this proposal.

PS2 P 16

Studying of gamma-ray and neutron radiation in case of 1 – 2 MeV proton beam interaction with various construction materialsI. Shchudlo¹, D. Kasatov², A. Makarov¹, T. Sycheva³, S. Taskaev¹¹*Budker Institute of Nuclear Physics, Novosibirsk* ²*Novosibirsk State University*³*Novosibirsk State Technical University, email: kasatovd@gmail.com*

In Budker Institute of Nuclear Physics it is proposed and created a source of epithermal neutrons based on the tandem accelerator with vacuum insulation and a lithium target. The neutron source is regarded as a prototype of a future compact device suitable for carrying out BNCT in oncology centers. It consists of two main parts: proton accelerator (2.5 MeV, 3 mA) and neutron-generating lithium target with a beam shaping assembly. Radiation hazard of the accelerator is determined by X-ray and gamma-ray radiation, but radiation hazard of lithium target is mainly determined by neutrons. When creating an optimal medical facility it is desirable to place these two parts in different rooms, adapted to suppress the corresponding radiation. The room of the accelerator should provide adequate protection against gamma-ray radiation even in case of emergency situation when the proton beam hits construction materials. In this work the measurements of the gamma-ray and neutron doses are presented in case of proton beam interaction (energy from 1 to 2 MeV) with various construction materials (Al, V, W, Ti, Cu, Mo, stainless steel, etc.). Also it is proposed an optimal construction material for beam transporting channel.

PS2 P 17

Development of an accelerator-driven compact neutron source for BNCT in Nagoya UniversityK. Tsuchida⁴, Y. Kiyanagi¹, A. Uritani², K. Watanabe², H. Shimizu³, K. Hirota³, M. Kitaguchi³¹*Research Laboratory of Accelerator-based BNCT system, Graduates School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8603*²*Department of Materials, Physics and Energy Engineering, Graduates School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8603*³*Laboratory for Particle Properties, Department School of Science, Graduates School of Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8602*

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Development of an accelerator-driven compact neutron source has been started in Nagoya University for BNCT application based on a low-energy high-current DC accelerator, which has also extra possibilities of applications to fundamental physics experiments and industry uses.

The accelerator is a Dynamitron and produces a 2.8MeV, 15mA proton beam [1] and neutrons will be produced by the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction. The resulting neutron flux will be moderated using a compact beam shaping assembly (BSA). From viewpoints of neutron production rates and the average and maximum neutron energies, it was reported that low energy protons incident on lithium target are the most suitable reaction for accelerator-based BNCT [2]. However, lithium target has several difficulties (low melting point, high chemical activity and ${}^7\text{Be}$ production) and we will develop a new Li-sealed target and a corresponded

BSA and evaluate their performances in combination with the Dynamitron as a compact neutron source for BNCT.

[1] E. Forton, F. Stichelbaut, A. Cambriani, W. Kleeven, J. Ahlback and Y. Jongen, "Overview of the IBA accelerator-based BNCT system" *Applied Radiation and Isotopes* 67 (2008) 5262-5265.

[2] J. Kim and K. Kim, "Current Research on accelerator-based Boron Neutron Capture Therapy in Korea" *Nuclear Engineering and Technology*, Vol.41, No.4 (2009) 531-544.

PS2 P 18

Study on the design of the miniature cyclotron for accelerator based BNCT

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The miniature cyclotron accelerator is designed by China Institute of Atomic Energy. Based on the accelerator and the Be target, the different proton energy changes with yield of neutron and the neutron yield changes with the Be thickness are calculated by MCNP. The optimization of configuration and material of the Beam-shaping-assembly (BSA) is also calculated by MCNP.

The neutron yield increases linearly when the proton energy between 10 Mev and 28 Mev will increase, and will decreases while the proton energy is more then 28 Mev. The relation between the neutron yield and Be thickness is calculated with the neutron energy of 10 Mev, 20 Mev and 30 Mev, the neutron yield will reach the saturation for 10 Mev when the Be thickness is more then 1 mm. According to the calculation results,

The proton energy with 10 Mev is selected as the design base of Beam-shaping-assembly, the final result is that the epithermal neutron flux rate generated by 10 Mev protons with 500 μ A current is 1.97 n/cm² s, the ration of fast neutron dose rate to epithermal neutron flux rate is 1.17×10^{-12} Gy cm², the ration of Gamma dose rate to epithermal neutron rate is 3.1×10^{-12} Gy cm², the ration of J to epithermal neutron flux rate is 0.63. The optimization of configuration and material of the Beam-shaping-assembly can meet the requirements for clinical treatment using the miniature cyclotron accelerator with 10 Mev proton and 500 μ A current.

PS2 P 19

Development of the injector for Vacuum Insulated Tandem Accelerator

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For development of the accelerator based BNCT concept it is proposed and developed the tandem accelerator with vacuum insulation. In the experimental tandem accelerator, built at Budker Institute of Nuclear Physics, the negative hydrogen ions are accelerated by the positive potential of the high-voltage electrode, converted into protons in the stripping target inside the electrode, and

further protons are accelerated again by the same potential. Entrance aperture of the accelerator is a strong electrostatic lens, which makes the beam injection more complicate. Existing injector includes the source of negative hydrogen ions, providing stable generation of up to 5 mA beam current, focusing solenoids, correctors. Vacuum volumes of the ion source and low energy beam line are pumped by turbomolecular pumps with the capacity of 1500 l/s and 450 l/s, respectively. The experiments presented that this injector configuration is not optimal: a long and narrow tube of low energy beam line leads to the significant neutralization of hydrogen ions by the residual gas, besides the stripping gas of the tandem accelerator can reach the ion source, affect to its work stability and contribute to the beam neutralization. To create the facility for therapeutic usage the accelerated beam current of 10 mA or higher is required. To provide the injection of such a current in the tandem accelerator new injector configuration is proposed with the ion source capable to generate of 15 mA beam and with preliminary beam acceleration up to 200 keV, which would make the beam transportation through the accelerator system more stable. The paper presents the design of the new injector with the calculations results.

PS2 P 20

Optimum design of a beam shaping assembly with an accelerator-driven subcritical neutron multiplier for boron neutron capture therapies

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It is most preferable that accelerator-based facilities for the production of treatment beam for the BNCT should be designed so that they are driven by small accelerators that generate protons of the energy below 5 MeV in low beam currents, since there are great benefits of easy construction of accelerators. The ${}^7\text{Li}$ (p, n) and ${}^9\text{Be}$ (p, n) reactions in this energy range have relatively large yields of neutrons and are suited for producing low energy neutrons. The author had designed a beam shaping assembly (BSA for abbreviation) equipped with the Be target driven by protons of the energy of 5 MeV, since higher proton energy leads to larger yield of neutrons and the Be target is much easier than the Li target to make and handle. However, the neutron yield per proton beam current is rather low and it turned out that high beam currents of the accelerator were needed to produce an adequate intensity of the treatment beam. For dropping the beam currents of the accelerator, the author studied a BSA that is combined with a subcritical neutron multiplier (SNM for abbreviation) equipped with the Be target driven by protons of the energy of 5 MeV.

Here, the SNM of $40 \times 37 \times 13 \text{ cm}^3$ in size fueled with 11.4 kilogram low-enriched uranium moderated by water was designed so that the BSA with the SNM had an effective reproduction constant (k_{eff}) of 0.990. The rectangular BSA prism including a part of the radiation shield is $120 \times 120 \times 135 \text{ cm}^3$ in size, and has a hole through the prism axis from end to end for the entrance of proton beam from the accelerator and the port of the treatment beam, and contains the Be target having an irradiation area of $12 \times 12 \text{ cm}^2$, the SNM in which neutrons multiply about a hundred times, the slabs of Pb and MgF_2 which have an area of $50 \times 50 \text{ cm}^2$ and make the proper neutron spectrum at the beam port, and so on. The dependence of the intensity of epithermal neutrons ($0.5 \text{ eV} < E < 10 \text{ KeV}$)

at the beam port on the thickness of the slabs of Pb and MgF_2 was examined so that the treatment beam fulfilled specific conditions under free-air where the contamination of absorbed dose by fast neutrons or photons is less than 3×10^{-13} or 2×10^{-13} [$Gy \cdot cm^2$], the ratio of thermal neutron flux to epithermal neutron flux is less than 5 %, the ratio of total neutron current to total neutron flux is more than 0.70, the dose equivalent rate on the radiation shielding at a distance of 25 cm from the treatment beam axis is less than 1 % of the value at the treatment beam axis.

When the Be target was driven by protons of the energy of 5 MeV in a beam current of 1 mA, the heat value of the SNM was estimated at 5.2 [KW]; the combination of a 11 cm thick slab of Pb and a 47.5 cm thick slab of MgF_2 produced the maximized epithermal neutron flux at the beam port of 0.95×10^9 [$1/cm^2/sec$] which was thirteen times as high as originally estimated value for the BSA without the SNM. These results imply that an adequate intensity for the treatment beam having the superior properties under free-air can be achieved by a SNM with a heat value of 10.4 [KW] as well as a small accelerator that generates protons of the energy of 5 MeV in a beam current of 2 mA. Further, the deposited power of 10 [KW] into the Be target may be effective in prolonging the life of the Be target and the heat density of 0.54 [W/cm^3] of the SNM should ensure the safe operation of this facility.

PS2 P 21

Optimal moderator materials at various proton energies considering residual radioactivity for an accelerator-driven $^9Be(p,n)$ BNCT neutron source

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BNCT has been performed mainly at research reactors, but it is not convenient since the place is far from the hospital. Therefore, to build BNCT facilities beside hospitals has been desired to make the treatment easier and popular. Nowadays, BNCT facilities based on accelerators have been constructed or planned by many research groups. Various proton energies have been proposed and major reactions for neutron production are p-Li and p-Be. Here, we consider p-Be since the Be target is much easier than the Li target to fabricate and handle. In Japan, two proton energies were used: the Kyoto University group used 30 MeV and the Tsukuba University group 8 MeV. Furthermore, the moderator materials used are different each other. This suggests that optimal moderator material depends on the proton energy. With increasing the proton energy the efficiency of the neutron production per proton become higher and the required beam power decreases; whereas higher proton energy leads to larger yield of fast neutrons and it will result in increase of residual radioactivity of a moderator, which depends on the material of moderator. Here, we have picked up the moderator material candidates: MgF_2 , CaF_2 and AlF_3 , since they had been widely used in the design studies of Beam Shaping Assembly (BSA). For studying proton energy dependence of optimal moderator materials, we calculated the required beam power and the residual radioactivity of a moderator in the BSAs.

When we design the irradiation system, we need filters for making an appropriate neutron beam. Here, we assumed two calculation models of the BSA. One consists of iron filter, moderator and collimator of polyethylene slab including lithium fluoride and lead slab. Another, layered composite filter made with lead, iron and aluminium, moderator and collimator same as the former. These filter materials were adopted in the Kyoto University system. We chose this filter since at higher proton energy aluminium is effective to decrease high energy neutrons. However, aluminium has a defect of high radioactivity. Therefore, we here studied two irradiation systems with and without aluminium. At various proton energies from 8 MeV to 30 MeV, we repeated following calculation procedure. First, we decided the thickness of moderator so that the fast neutron component of the incident beam becomes a value less than 1.0×10^{-12} [Gy cm²]. Then we calculated the proton beam current to produce the epithermal neutron flux of 1.5×10^9 [1/cm²/sec] at the outlet of the collimator. Further, we calculated the residual radioactivity of the moderator and the dose equivalent rate around the moderator.

At lower proton energy, it turned out that the required beam power became low in the case of MgF₂. Magnesium has good moderating effect, decreasing fast neutron component at the thinnest thickness and the beam power is the lowest. Furthermore, the activation is sufficiently low to work at a place near the collimator. On the other hand, at higher energy region over about 11 MeV, CaF₂ is the optimum material especially in terms of the activation. For example, at the proton energy of 11 MeV, γ-dose rate from iron filter and moderator at an hour after the irradiation is about 10 μSv/h in the case of CaF₂, whereas they are 120 μSv/h in the case of MgF₂ and 50 μSv/h in the case of AlF₃. The reason of high radioactivity is ²⁴Na produced by ²⁴Mg(n,p)²⁴Na or ²⁷Al(n,α)²⁴Na.

PS2 P 22

Neutron Activation and Exposure Estimation of a Lithium Target Design

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Accelerator-based BNCT (AB-BNCT) is considered as the future of BNCT development. Various AB-BNCT designs have been developed and evaluated. This work aims to evaluate a rarely discussed topic of AB-BNCT design – the activation and dose exposure to worker of target station.

Among the many AB-BNCT designs, lithium and beryllium are the 2 most used materials to generate neutrons via protons. The discussed target in this study is a lithium based one. The target was irradiated by a 10-mA, 2.5-MeV proton beam. The workload was assumed to be 30 minutes per irradiation, 20 minutes between two irradiations, and 10 irradiations per day. The lithium layer was coated on a copper base, through which cooling water travels. Threshold reaction was not discussed in this study because the incident proton beam energy is so small and so the induced neutrons. Hence, there is no threshold reactions occurred in the target, or only very limited amount of activation induced.

The main traced activated nuclides are ⁷Be, ²⁸Al, and ⁶⁴Cu. Corresponding radioactivities and doses caused by these radioactive nuclides were calculated

by using MCNP6. Among the 3 calculated nuclides, only ${}^7\text{Be}$ ($T_{1/2} = 53.2$ days) is considerable to worker dose exposure because the half-life of the other 2 nuclides are short and will fade out after a reasonable cooling time. The dose rate to a worker who changes the target was calculated at different distances away from the target, with and without an additional lead shielding around the target when removing.

The saturated activity of ${}^7\text{Be}$ is ~ 207 Ci under the given condition described above. However the target will break before reaching the saturated activity because of blistering problem occurred in copper base. A more reasonable estimation is ~ 15.7 Ci when the target has to be replaced. According to this activity, the calculated results showed the dose rate without lead shielding at 3 cm reaches 4788 mSv/hr conservatively, and at 10 cm away from the target surface it is 431 mSv/hr; the dose rate decreases to 48 mSv/hr at 30 cm. When a 3-cm thick lead shielding was applied, the surface dose rate is 215 mSv/hr, and 9.75 mSv/hr for 5-cm thick lead shielding.

Although the activity of ${}^7\text{Be}$ is quite high, its decay energy is not high and can be effectively shielded by lead. The gamma ray from electron capture is of 477.6 keV and its branch ratio is only 10.44%. From the estimated results, an addition 5-cm thick lead shielding should be applied to the target when replacement. The worker should be equipped with mobile shielding and remote-operation tools or hand shielding to reduce the exposure to an acceptable level. Precaution must be taken for the sake of personnel protection when using lithium as the target material.

PS2 P 23

A comprehensive study on ${}^9\text{Be}(d,n){}^{10}\text{B}$ -based neutron sources for skin and deep tumor treatments.

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The ${}^9\text{Be}(d,n){}^{10}\text{B}$ reaction has been thoroughly studied as a possible neutron source for Accelerator-Based BNCT. For bombarding energies ranging from 1 to 1.5 MeV, the neutron spectrum produced by this reaction shows a strong contribution of neutrons of a few hundred keV and a "tail" that extends up to 5-6 keV. The strong contribution in the low-energy range of the spectrum belongs to the population of a group of excited states at about 5 MeV in the residual nucleus ${}^{10}\text{B}$. These states are energetically accessible for deuteron energies of about 1 MeV and are preferentially populated as compared to the lowest-energy states in ${}^{10}\text{B}$. Here, the use of a thin target appears as an interesting approach for softening the neutron spectrum. In a thick target (i.e., thickness larger than the range of deuterons in Be) a deuteron loses all the energy as it penetrates the target. Therefore, most of the (d,n) reactions occur at a bombarding energy lower than the 1 MeV threshold, where only the lowest energy states in ${}^{10}\text{B}$ can be populated. Consequently, most of the neutrons produced in a thick target contribute to the "tail" of the spectrum. In contrast, if the target is thin enough so that the residual energy of the deuterons after traversing the target is higher than 1 MeV, all the reactions

that occur below the energy threshold are removed, and hence, the neutron production associated with the tail of the spectrum is significantly reduced.

The ${}^9\text{Be}(d,n){}^{10}\text{B}$ reaction produces a softer neutron spectrum compared to the one coming from fission but a harder one compared to the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction, even using a thin target. However, the excellent mechanical and thermal properties of the target material plus the absence of residual radioactivity make of the ${}^9\text{Be}(d,n){}^{10}\text{B}$ a better candidate for a neutron source concerning target engineering and cooling requirements compared to the lithium reaction.

In this context, a thorough Monte-Carlo simulation study aimed at assessing the treatment capability of ${}^9\text{Be}(d,n){}^{10}\text{B}$ -based neutron sources was carried out. For this purpose, a comprehensive compilation of the existing data about double-differential cross-sections was carried out at first, which allowed us building realistic primary neutron field models. In addition, measurements of the double-differential neutron production were carried out for some bombarding energies in the range of interest.

Two kinds of neutron sources were evaluated. First, neutron spectra produced by thin targets were used to assess deep-tumor treatment capability. A thorough investigation on the optimal combination of bombarding energy and target thickness was carried out. Our best-case result showed that it is possible to achieve dose performances comparable to some phase I/II clinical trials carried out with reactor-based sources and to a ${}^7\text{Li}(p,n){}^7\text{Be}$ -based neutron source. Secondly, the measured spectra produced by a thick target and deuterons of 1.2 and 1.35 MeV were evaluated for skin tumor treatments. In this case, dose performances resulted comparable to those achieved in melanoma treatments at the RA-6 nuclear reactor in Argentina. These promising results strengthen the prospects for a potential use of the ${}^9\text{Be}(d,n){}^{10}\text{B}$ reaction and for the implementation of an operational AB-BNCT facility in Argentina.

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Progress in the design and development of a neutron production target for Accelerator-Based Boron Neutron Capture Therapy

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As part of a project for developing Accelerator-Based Boron Neutron Capture Therapy (AB- BNCT) for which the generation of neutrons through nuclear reactions like ${}^9\text{Be}(d,n)$ is necessary, a high power neutron production target is being designed and developed at CNEA facilities. Here we show the first results for such work.

To produce the neutron beam suitable for AB-BNCT, the Be target will be hit by a deuteron beam of 1.4 MeV with a current of about 30 mA. Under such conditions, the target has to be able to withstand the mechanical and thermal

stresses produced by such an intense beam. In particular, the target should be able to dissipate an energy density of up to 1 kW/cm² and preserve its physical and mechanical properties and integrity for a sufficient length of time under irradiation and hydrogen damage conditions.

Surface treatments of different backing materials were made, like blasting and metal deposits to favor the affinity between Beryllium and the substrate, and stable deposits were obtained. These stable Be deposits, made on different substrates, were characterized by means of different techniques including Scanning Electron Microscopy (SEM), roughness, thickness, etc.

As previously mentioned, the target will have to withstand an intense deuteron beam in order to satisfy the power dissipation requirements for the neutron production target. Microchannel system simulations in a turbulent flow circulation regime using the physical model proposed in the literature are presented. The results obtained were compared with those in several publications and discrepancies lower than 10% were found in all cases.

Fluid dynamics and structural mechanics simulations were carried out and are discussed in this paper. These simulations allow the determination of geometric parameters of the prototype complying with the requirements of a microchannel system. Such simulations allow us to design a validation prototype, which is being constructed using the knowledge acquired in this work.

PS2 P 25

A beam line for BNCT at the European Spallation Source ESS

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The European Spallation Source (ESS)

Seventeen European countries are working together to build a leading research facility of unparalleled power and scientific performance for materials and life science with neutrons – the European Spallation Source (ESS). ESS is a multi-disciplinary research center based on the world's most powerful neutron source. This new facility will be around 30 times brighter than today's leading facilities, enabling new opportunities for researchers in the fields of life sciences, energy, environmental technology, cultural heritage and fundamental physics. The facility design and construction includes a linear proton accelerator, a heavy-metal target station, a large array of state-of-the-art neutron instruments, a suite of laboratories, and a supercomputing data management and software development center. The ESS facility is under construction in Lund, whilst the ESS Data Management and Software Center will be located in Copenhagen. A total of 22 beam-lines with dedicated detectors is foreseen to be built at the ESS, with the aim of having the initial seven instruments online with the first neutrons in 2019 and the full suite installed in 2025. The instruments built at ESS are selected from among instrument concepts being developed at different labs. This selection

is done through a call for proposals, followed by a review that engages expert reviewers from around the world. Several instrument concepts are chosen for construction each year.

Preparation of an instrument concept proposal for BNCT

¹Instead of the successful European efforts and research projects on BNCT in the late 90ies and the last decade, there is nowadays no neutron beam for BNCT available in Europe. Compact accelerators producing high intensity epithermal neutron beams and that can be based at hospitals will be realized in the near future and might be an important contribution to clinical research. However basic research activities that are mandatory for any further development in BNCT need a multidisciplinary approach at the highest scientific level. A perfect host for such a scientific platform would be the ESS. Special efforts have to be made for its realization. In a first step a users community will have to be identified and a strong scientific case will have to be made. To open the discussion, a first meeting will take place during ICNCT16. A second workshop will be organized in Essen (Germany) end of this year to prepare further an instrument concept proposal for BNCT. Everybody interested in such a development is invited to participate.

PS2 P 26

Safety analysis of the uranium neutron converter for BNCT facility

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Research stand of epithermal neutron beam using neutron converter is prepared in the National Centre for Nuclear Research in Świerk, Poland. Converter, built with fuel rods EK-10, containing low enriched uranium (10 % ²³⁵U), is used to modify the energy spectrum of primary neutron beam. Analysis includes physics calculations (neutron), heat-flow in steady state and transient condition, activity of fission products, and radiological hazard of the emitted gamma rays.

As a preliminary examinations there were performed a leak tests of fuel rods placed inside the converter and measurements of the abrasive surface contamination (alpha contamination). In order to determine the heat generation in the fuel EK-10 in the converter, the calculations of neutron reactor core MARIA with converter containing 99 fuel rods were performed. To specify thermo-hydraulic characteristics in steady states it was necessary to calculate the hydraulic resistance of the neutron converter, heat transfer, flow rates and heat removal from the converter. Analyses of the activity of the converter fission products were performed to determine the gamma-ray sources for the further calculation of the converter shielding. There were defined the most important fission products' activities, contained in the fuel rods EK-10 after long-term cooling of the converter. Analysis covered also the shielding and radiological exposure risk for personnel during reloads and transport operations. There were estimated the change of the dose rate above the water and shieldings at front wall of the disassembly chamber and lead sight glasses.

It was examined how the reactor transient states associated with the introduction of positive reactivity affect the operating conditions of the converter. It has been proven that uranium converter does not affect the reactivity of the reactor core

MARIA, while changes in reactor power due to the interference of reactivity imply changes in the thermal power dissipated in the converter. It was also examined how the reactor transient states associated with a decrease in the ability of the reactor core cooling effect on operating conditions of the converter.

Analysis of the radiological risk associated with damage to the rod EK-10 in the converter was performed too. Shielding calculations indicated that radiological hazard to personnel is minimal for both the reload and transport operations in pool and in the disassembly chamber of the reactor. The only operational limit that is required during operation of the converter with EK-10 uranium fuel in the MARIA reactor is to maintain a certain pressure drop for the core matrix.

PS2 P 27

Design of an epithermal BNCT system using a compact coolant moderated neutron generator

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Compact accelerator driven neutron generators using the deuteron-deuteron (D-D) and deuteron-triton (D-T) fusion reaction offer many advantages for use in BNCT applications. Using a microwave driven ion source, ion currents exceeding 200 mA/cm² are easily achievable using the ECR resonance plasma discharge. In the D-T neutron generator, the mixed deuteron/triton ion beam is accelerated to ~150keV and bombard a titanium loaded target to generate 14MeV neutrons via the ³H(d,n)⁴He reaction. Neutron yields on the order of 2E12 neutrons/second are possible with uptime exceeding 99 % using a Fluorinert cooled target. The resulting 14MeV neutrons are optimally moderated by the Fluorinert to produce a high fraction of epithermal neutrons (0.4 – 10 keV) with flux >2E8 n/cm²/s. This desktop sized neutron generator should be an attractive tool for performing BNCT in a hospital environment.

PS2 P 28

DECISIONS AND PREPARATIONS FOR A RAPID SHUTDOWN AND DECOMMISSIONING OF THE FINNISH TRIGA FIR 1

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VTT Technical Research Centre of Finland as the licensee of the government owned FIR 1 TRIGA research reactor decided in July 2012 to close down the FIR 1 reactor as soon as it is technically and legislatively possible. The income from the reactor services has not covered all the costs of the reactor and VTT is not willing to cover this deficit any more. The juristics and required concrete actions are clarified. Currently an environmental impact assessment (EIA) of the decommissioning is conducted as a prerequisite for the application to the

government for shutting down of the reactor. The current estimate is that the shutdown could take place at the earliest autumn 2015.

The events leading to this decision by VTT are clarified. The role of VTT as the licensee and the role of government and the ministries is discussed.

The alternatives to be assessed in the environmental impact assessment are described. In the "0" option the reactor will continue operation. Alternative administrative and funding arrangements that would allow continuation of reactor operations are discussed. In the alternative A1 an immediate dismantling of the reactor will follow the shutdown. Possibilities to utilize the BNCT facility components at other reactors are discussed. These include the beam shaping assembly with the FLUENTAL™ neutron moderator, the modular heavy concrete and lithiated plastic shielding of the patient irradiation room. Also the patient positioning system could be utilized elsewhere.

PS2 P 29

Narrow Neutron Beam Assembly Facility in BNCT Application

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BNCT is known as an effective technique to selectively destroy malignant tumor cells. In order to be successful, a sufficient amount of ^{10}B must be selectively delivered to all tumor cells ($\sim 20 \mu\text{g/g}$ weight or $\sim 10^9$ atoms/cell), and enough thermal neutrons must be absorbed to cause lethal damage from $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction [Rolf Barth et al. Radiation Oncology 2012, 7:146]. The destructive effects of reaction ions with very short path lengths in tissues ($5\text{--}9 \mu\text{m}$), in theory BNCT provides a way to selectively destroy malignant cells. Clinical interest in BNCT has focused primarily on high grade GBM and more recently on patients with recurrent tumors of the head and neck region who have failed conventional therapy.

The only two BNCT delivery agents currently used in clinical trials are BSH, BPA. Neither of these agents adequately fulfills the criteria indicated above, and for this reason third generation agents have been investigated. The major challenge in the development of such agents has been the requirement for selective tumor cell targeting and the delivery of therapeutic boron levels with minimal normal tissue toxicity.

After almost 25 years, more recent clinical trials were initiated at MIT and BNL, in the early 1990's, using for the first time higher energy neutrons in the epithermal energy range ($\sim 0.4 \text{ eV} \leq E \leq 10 \text{ keV}$). These higher energy neutrons obviated the need for intra-operative BNCT when treating deep seated malignancies. Epithermal neutrons, for example, can reach tumors at the midline of the brain at a depth of $\sim 8 \text{ cm}$. Epithermal neutrons are now generally used in BNCT irradiations although some intra-operative irradiations with thermal neutrons are still performed. Reactor-based facilities in Japan are capable of producing various mixtures of thermal and epithermal neutron spectra, which can be advantageous for head and neck cancers where deep beam penetration may not be required.

In cancer therapy using BNCT, three components are involved, namely energy dependant neutron flux $\phi(r,E)$, ^{10}B atomic density $N_{\text{B}}(r,t)$ and ^{10}B effective microscopic cross section $\sigma_{\text{c}}(E)$. The capture interaction is: $R(r,E,t)=N_{\text{B}}(r,t)\sigma_{\text{c}}(E)\phi(r,E)t(s)$. In our experiment after boron solution was injected transcidentally via left ventricle in rats, it took 4h ^{10}B concentration reaches maximum in rat's brain. Then ^{10}B density declines because of two factors: biological half-life. Capture cross section of ^{10}B is 1/V absorber from 10^{-5} eV to 0.5MeV, and the standard cross section is 3842.56b at 0.0253eV. $N_{\text{B}}=10^9$ atoms B/cell; $(E=0.025\text{eV})=3842.56\text{b}$; $\phi(r,E)=10^9\text{n/cm}^2\cdot\text{s}$; $t=1000\text{s}$. It is seen in the best conditions 4 reactions/cell occurs. It should be bear in mind, (1) tumor temperature is about 40°C and (2) neutrons impinging tumor cells are not Maxwellian distribution. As a result, ^{10}B effective cross section is much smaller than 3842.56b and hence number of captures is even less than one. Another issue is the neutron beam energy range $0.4\text{eV} < E < 10\text{keV}$. Depending on tumor depth and width, proper neutron energy band has to be used. This is a serious issue, since the neutron beam should wide enough to embrace the tumor. But in practice many of the neutrons just pass through normal cells and may have destructive effects on the cells. One should keep in mind that some of the high energy neutrons just scatter out of tumor. In order to overcome this effect, it is better to take advantage of bunch of narrow neutron beam with the capability of scanning back and forth with adjustable neutron beam intensity. This bunch of narrow neutron beams is quite manoeurable to move around without affecting normal cells.

PS2 P 30

A study of photoneutron source based on electron accelerator including heat transfer using the jet impingement cooling method

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Abstract

The objective of this paper is to design a photoneutron source based on electron accelerator considering the efficient heat removal from an e- γ converter. In this source dimensions of electron/photon and photoneutron targets including radius and thickness are optimized to obtain maximum value of the neutron yield using the MCNPX code. In the simulations, tungsten is used as the bremsstrahlung production target and heavy water serving as the dual purpose of photoneutron production and heat exchange medium. As expected, by increasing the electron current the photoneutron flux and also the temperature of tungsten are increased. In order to control the temperature, a jet impingement cooling method is used. The distributions of the velocity and temperature in the system are calculated using computational fluid dynamics method. The results show that the neutron yields reach up to 10^{11} n/mA/s and 10^{12} n/mA/s with a mean energy of 0.24 MeV and 0.55 MeV for 5 and 10 MeV electrons, respectively. Furthermore, it can be found that the jet impingement cooling method is applicable and effective to design this kind of systems.

Thursday June 19th

Pa P6 01

The Response of ESR Dosimeters in Thermal Neutron Fields

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ESR dosimetry is based on the measurement of radiation induced radicals. Alanine is the best known ESR-detector and former results proofed the applicability in neutron fields. However the separation of dose components is difficult and only possible using Monte Carlo Simulation. Formate or carbonate salts can be used alternatively. The cation in such salts can have high cross sections for the production of secondary, dose-depositing particles and is easy to vary. Therefore the possibilities have been investigated to identify dose components by comparison of detectors of different composition.

Ammonium-, Calcium- and Lithium-formate as well as Calcium-carbonate detectors have been irradiated in the mixed neutron and photon field of the thermal column of the research reactor TRIGA Mainz, Germany. The column is completely filled with graphite and provides predominately thermal neutrons. Read-out of the dosimeters has been performed with Electron Spin Resonance Spectrometry using photon calibration. Absorbed doses and dose components have been calculated using the Monte Carlo Code FLUKA. In conjunction to this, considerations towards the Relative Effectiveness (RE) have been made using the Hansen & Olsen detector response model. RE takes account for the nonlinear dose response towards particle species and energy.

The measured dose response of the dosimeters in different experiments will be shown and compared to model predictions. RE values and calculated dose components will be discussed with the measured data. A comparison between the different detector materials and the previous alanine results show the potential for field characterisation in arbitrary mixed neutron and photon fields.

Pa P6 02

Determination of gamma component in thermal column of Pavia Triga reactor by using alanine ESR detectors

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The development of Neutron Capture Therapy (NCT) for cancer treatments has stimulated the research for beam characterization in order to optimize the therapy procedures. One major issue for this kind of therapy is the reliable dosimetric determination of the various (neutronic and photonic) components of the employed beam. In particular, the precise and accurate measurements of the gamma photons component are fundamental for evaluating the risks to healthy tissues hit by the mixed field.

Among solid state dosimeters the alanine EPR detectors present several advantages such as: tissue equivalence, linearity of its dose-response over a wide range, high stability of radiation induced free radicals, no destructive read-out procedure, no sample treatment before EPR signal measurement and low cost of the dosimeters. These features associated with the possibility of recognizing the various components of a mixed radiation fields makes alanine a good candidate for dosimetry in neutron-gamma fields.

In this work we determine the gamma component of the mixed radiation field in thermal column of the Triga reactor of University of Pavia (which is used for experimental activities on BNCT) by means of electron spin resonance (ESR) alanine dosimeters.

Commercial alanine dosimeters produced by Synergy Health (Germany) were exposed in three positions in the thermal column; the irradiations were performed inside graphite holders to avoid use of hydrogenous phantoms. ESR measurements were carried out through Bruker ECS106 spectrometer equipped with a TE₁₀₂ rectangular cavity.

Monte Carlo computations with the MCNP code were carried out by modelling the reactor geometry and the irradiation set-up. With these analyses we gained information about the contributions of the various components present in the mixed neutron-photon field.

In order to isolate the gamma components of the mixed field two kinds of irradiations were carried out inside a lithium carbonate box and outside of it.

The experimental values are compared with the Monte Carlo simulations and the results are discussed on the basis of the mixed field features and on the response of alanine dosimeters to high and low LET radiations.

Pa P6 03

Phenol compounds for Electron Spin Resonance dosimetry of gamma and neutron beams

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The development of Neutron Capture Therapy (NCT) for cancer treatments has stimulated the research for beam characterization in order to optimize the therapy procedures. Reliable dosimetric measurements should be able to determine the various components (neutronic and photonic) of the mixed beam usually employed for therapy.

In this work we study the response of phenolic compounds with and without gadolinium addition for electron spin resonance (ESR) dosimetry exposed to a gamma and mixed (n, gamma) field mainly composed of thermal neutrons. In particular, the phenol octadecyl-3-(3,5-di-tert.butyl-4-hydroxyphenyl)-propionate gave interesting results. In fact, this compound gives a phenoxy radical stabilized by the presence of two bulky groups. Moreover, its high molecular weight, the low volatility and the compatibility with the dosimeter binding material (wax) are advantages with respect to lower molecular weight phenols.

The choice of Gd as additive nuclei is due to its very high capture cross section to thermal neutrons. Furthermore, after the nuclear reaction with thermal neutrons particles, which in turn release their energy in the neighbourhood of the reaction site, are ejected.

The dosimetric features of these ESR dosimeters have been investigated. In particular, we analyzed the ESR spectra of these compounds and their dependence on microwave power and modulation amplitude, their response after gamma and neutron irradiations, the detection limits for both beam typologies, signal stability after irradiation.

Pa Ch3 01

Boron-rich Liposomes as Nanoscale Delivery Agents for BNCT

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The application of boron neutron capture therapy (BNCT) mediated by boron-rich MAC-TAC-liposomes or boron-rich polymeric nanoparticles in two mice tumor models, the murine mammary carcinoma cell line EMT6 and the mouse colon cancer cell line CT-26 will be presented. One of the requirements for successful BNCT is selective delivery and retention of ¹⁰B in the tumor tissue while minimizing superfluous ¹⁰B within the surrounding healthy tissue. MAC-TAC-liposomes target tumor cells using the enhanced retention and permeation (EPR) effect and selectively deliver a therapeutic concentration of ¹⁰B to the tumor tissue with a high tumor to blood boron ratio. Our laboratory has extensively studied unilamellar liposomes constructed with a variety of boron species and evaluated their *in vivo* performance.

In the EMT6 tumor model, two tail vein injections 24 h apart of liposomes containing an amphiphilic [KC₂B₉H₁₁(CH₂)₁₅CH₃] (MAC) in the lipid bilayer and

a hydrophilic [$\text{Na}_3\text{B}_{20}\text{H}_{17}\text{NH}_3$] (TAC) in the aqueous core deliver up to 70 ppm of boron to the tumor tissue along with a very favorable tumor to blood boron ratio 54 h following the initial injection. Similarly, in the case of the CT-26 cell line, the MAC-TAC-liposomes were able to deliver more than 50 ppm of boron to the tumor tissue, also with a high tumor to blood boron ratio. Neutron irradiation for 60 min (3.2×10^{12} neutrons per cm^2) using the University of Missouri thermal neutron beam resulted in significant suppression of both EMT6 and CT-26 tumors. No apparent radiotoxicity was observed.

In the course of our study we observed that tumors with a mass less than 150 mg had a higher percentage of boron than in larger tumors which normally contain necrotic tissue in the tumor center. Micro-distribution of boron in the tumor tissue was investigated using Matrix Assisted Laser Desorption Imaging (MALDI) mass spectrometry. A 10-micron slice of the tumor tissue from mice injected with MAC-TAC-liposomes 30h prior to the excision of the tumor was mounted on the glass plate, coated with a suitable matrix and irradiated with a laser. The resulting ions were analyzed by FT-MS for the presence of MAC and TAC. Tumors larger than 150 mg had a higher concentration of boron on the periphery of the tumor, whereas smaller tumors showed a homogeneous distribution of boron. In a related *in vitro* localization study of MAC and TAC components in EMT6 cells, the results indicate that the TAC component is predominantly located in the lysosomes while the MAC component is incorporated in the cell membrane.

To better understand how boron concentration affects the outcome of BNCT therapy, in an *in vitro* boron dose escalation study we investigated the effect of boron concentration on cell survival upon thermal neutron irradiation. Varying the boron concentration while keeping a fixed thermal neutron irradiation dose, we observed that approximately 50 ppm of ^{10}B is sufficient for effective BNCT.

Boron-rich polymeric nanoparticles for the delivery of a high concentration of ^{10}B to tumor tissue were generated through a radical-initiated emulsion polymerization of a mixture of monomers (one of which contains a polyhedral carborane) resulting in a dense spherical core. The nanoparticle surface was coated with polyethylene glycol to assist the nanoparticle in evasion of the reticuloendothelial (mononuclear phagocyte) system and thus increase their circulation time. These nanoparticles contain approximately 33 % of natural abundance boron by weight. The biodistribution studies of boron-rich nanoparticles in mice showed more than 150 ppm of natural abundance boron in the tumor tissue, which corresponds to approximately 30 ppm of ^{10}B isotope. The percentage of ^{10}B isotope can be adjusted by varying the amount of enriched ^{10}B monomer in the nanoparticle formulation.

Pa Ch3 02

Design and Synthesis of Tumor Seeking *closo*-Dodecaborate-Containing Amino Acids as Boron Carrier for BNCT

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In the development of useful boron carriers for BNCT, unusual boron amino acids represented by *L-p*-boronophenylalanine (BPA) have long been recognized as tumor seeking compounds due to structural analogy to usual L-amino acid, because L-amino acid transport system is enhanced compared with normal tissues to sustain the proliferation of tumor cells. On the other hand, dodecaborate ($[B_{12}H_{12}]^{2-}$), the mother nucleus of mercapto-*closo*-dodecaborate (BSH) and ammonio-*closo*-dodecaborate (BH_3), is a versatile and available boron cluster bearing high boron occupancy. We have already reported the syntheses of various types of *closo*-dodecaborate ($[B_{12}H_{11}]^{2-}$) unit containing amino acids by the coupling reaction of *closo*-dodecaborate derivatives with halogenated L- α -amino acid derivatives. As an extension of this work, we report herein useful methods for the syntheses of a novel class of *closo*-dodecaborate-containing amino acids, and also report their biological evaluation as boron carrier for BNCT.

First we designed and synthesized two types of thio-*closo*-dodecaborate ($[B_{12}H_{11}]^{2-}$ -S-) unit containing α -alkylamino acids $\{[B_{12}H_{11}]^{2-}$ -S-(CH₂)_n-CH(NH₂)COOH **I**\} and α , α -cycloalkylamino acids $\{[B_{12}H_{11}]^{2-}$ -S-CH₂-(cyclo-CH₂)_n-C(NH₂)COOH, n=4, 6 **II**\} by S-alkylation reaction of BSH in short step sequence. The *in vitro* evaluation of the cytotoxicity, cell-killing effects, and micro-distribution analysis by immunocytochemical technique suggested that these **I** and **II** might be a potential lead compounds to develop novel boron compounds for BNCT.

A new class of ammonio-*closo*-dodecaborate-containing amino acid derivatives illustrated as $\{[B_{12}H_{11}]^{1-}$ -NH₂CO-CHR(NH₂), R=Me, *i*-Pr etc. **III**\} was synthesized according to our reported method. The direct amide-bond formation of **III** was performed in one pot reaction by using amino-*closo*-dodecaborate prepared from ammonio-*closo*-dodecaborate and activated amino acid esters in moderate yields. This class amino acid is to be advantages over thio-*closo*-dodecaborate amino acid in tumor cell affinity due to its reduced negative charge (-1). The biological activities of **III** are currently confirming.

Pa Ch3 03

Kojic Acid Modified α -Carborane/Hydroxypropyl- β -Cyclo-dextrin Complex as Novel BNCT Drug for Melanoma

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Treatment of metastatic malignant melanoma remains ongoing challenges. Boron neutron capture therapy (BNCT) is single cell-selective radiation therapy for cancer. Therefore, BNCT has been attracted great deal of attention as a potent modality for malignant melanoma. The success of BNCT depends on the boron delivery system to accumulate effectively and deeply inside the tumor cells. Boronophenylalanine (BPA) and Sodium borocaptate (BSH) are currently used for BNCT as boron carriers. However, these compounds have some disadvantages on accumulation, water-solubility, or selectivity toward tumor tissue. On the other hand, it has been well known that kojic acid possesses a whitening activity to melanocytes by a strong tyrosinase inhibition. This fact suggests that kojic

acid could act as effective ligand for melanoma-targeting. In order to develop a novel boron delivery system for melanoma-targeting BNCT, we utilized kojic acid modified *o*-carborane (CKA). Because CKA shows poor water-solubility, various cyclodextrins were estimated as a solubilizer. Since the inclusion complex of hydroxypropyl- β -cyclodextrin (HP- β -CD) provides the highest concentration of CKA solution, herein, the CKA/ HP- β -CD complex was evaluated as boron drug for melanoma-targeting BNCT.

Water-soluble CKA complexes were effectively prepared with HP- β -CD by using mixing with vortex-mixer. After addition of CKA/HP- β -CD to culture medium of B16BL6 (murine melanoma), C2C12 (murine myoblast), and colon26 (murine colorectal cancer), relative cell viability was estimated in 24 hours. CKA/HP- β -CD shows little toxicity under 40 ppmB. Therefore, Cellular uptake and cellular distribution of CKA/HP- β -CD were evaluated within 10 ppmB. CKA/HP- β -CD was taken up more efficiently by B16BL6 than C2C12 and colon26. Uptake by B16BL6 was inhibited with excess free kojic acid/HP- β -CD complex. These results indicate CKA/HP- β -CD possesses melanoma affinity and selectivity. Moreover, CKA/HP- β -CD was localized at nucleus in 1 hour after treatment. The fact that CKA/HP- β -CD is localized to the nuclei is so significant that the therapeutic efficacy of BNCT could be improved by efficiently performing DNA double strand break.

The therapeutic and antitumor efficiency of CKA/HP- β -CD were evaluated by using tumor-bearing mice implanted with B16BL6 cells. CKA/HP- β -CD and L-BPA fructose complex were injected by intraperitoneal administration before 1 hr of irradiation. Neutron irradiation was carried out at Kyoto University Research Reactor (5 MW, 18 min, 5.0×10^{12} neutron/cm²). By irradiation, proliferation and antitumor efficiency of BNCT were improved within concentration-dependent and neutron fluence-dependent. Moreover, CKA/HP- β -CD shows similar or superior tumor suppression effect to L-BPA.

In summary, CKA/HP- β -CD complex can deliver boron atoms toward melanoma selectively and effectively. Therefore, CKA/HP- β -CD complex can improve the survival of the tumor-bearing mice as effective as L-BPA. This boron carrier is promising for melanoma BNCT.

PI P2 01

Development of the linac based NCT facility in iBNCT project

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A project team (iBNCT project) headed University of Tsukuba is driving forward the development of an accelerator based neutron source for BNCT. The iBNCT project team consists of University of Tsukuba, High Energy Accelerator Research Organization (KEK), Japan Atomic Energy Agency (JAEA), Mitsubishi Heavy

Industry Ltd. and Ibaraki prefecture. We are developing a high intensity linac based neutron source as well as several treatment devices like treatment planning system.

In iBNCT project, we have employed RFQ+DTL type linac as proton accelerator. Energy of the proton beam is specified to 8 MeV. And we have selected beryllium as neutron target material. Reaction with 8 MeV proton and beryllium emits only comparatively low energy neutrons (< 6.1 MeV) and then the neutrons hardly occur incidental reaction with several materials formed the treatment devices. Therefore the combination of the 8MeV proton and Beryllium enables to avoid heavy activation of the neutron generator such as Be, moderator and collimator. To generate enough epithermal neutrons, average beam current of the accelerator is specified to 10mA in maximum.

The linac is designed by KEK. And Mitsubishi heavy industry manufactured the RFQ and DTL tubes. Several incidental equipment of the linac as klystron and power supply is also manufactured by several companies. To generate enough neutrons for BNCT, the maximum proton power of 80kW is irradiated to the beryllium target as described above. Thus the huge heat deposition in the beryllium is a big issue. And we have to also avoid target breakage caused by blistering with the huge proton irradiation. To solve the target issues, the neutron source device with beryllium target is being developed in collaboration with KEK, Mitsubishi and some companies. Finally a prototype of the target system has been just completed.

At present, we are also designing a neutron generator device consisting of Be target, moderator, collimator and radiation shield. To determine conceptual design of the device, Monte-Carlo analysis using the multi-purpose Monte-Carlo code; PHITS is being performed. Results of the Monte-Carlo analysis, Fe filter was set to behind of the beryllium target to cut the high energy neutrons. And MgF_2 was employed to moderator in order to reduce moderate high energy neutron to epithermal neutrons. The collimator and neutron shields was constructed by lead, concrete and polyethylene with LiF. The results of the Monte-Carlo analysis indicated that the neutron generator with 80kW proton beam can emit enough epithermal neutron flux as approximately 4.6×10^9 (n/cm²/s) at the beam port. At present, we are manufacturing the neutron generator in accordance with the conceptual design.

In the project, we are developing not only the linac based neutron source but also medical equipment required in BNCT such as treatment planning system, patient setting device and radiation monitors.

Ion source of the linac has begun to work and to accelerate proton beams to 50 keV in March in 2014. In current schedule, the neutron generator will be completing in summy in 2014. And finally, first clinical trial using the linac-based BNCT device is planned to be performed within 2015.

PI P2 02

Development of treatment couch with computer controlled 5-axis movements - For clinical use in the accelerator-based BNCT

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Introduction

National Cancer Center (Tokyo) started a joint research with CICS in Dec. 2010 and is planning the installation of the accelerator-based BNCT system. New building for BNCT was finished in Dec. 2013 and accelerator installation is expected in May this year. We are now stepping to the next stage in medical use of BNCT. Simultaneously we developed treatment couch for the accelerator-based BNCT.

Materials and Methods

Three basic mechanisms were assumed. Treatment couch is compatible with CT-based treatment planning and detachable to be transported to the BNCT treatment room. According to the treatment planning with the optimal patient positioning, the couch moves in 5 axes and lifts the patients to the BNCT beam outlet in the optimal body positioning.

Results

The patient is fixed with vacuum lock system to the couch comfortable. From the CT acquisition to the actual treatment, the patient does not need to move himself to take the optimal BNCT body positioning. Because of the round shape of the beam outlet, 5-axis movements of the couch could bring the patient to the optimal position. Skin marking by laser projector was useful to verify the reproduction of the body positioning according to the BNCT treatment plan.

Conclusion

Development of clinically applicable treatment couch for BNCT was successfully accomplished. However, the treatment planning information is presently input off-line and the system is not DICOM-RT-based. Additionally real-time position change is desirable. Version up of the system is already being launched.

PI P2 03

Ex-situ lung BNCT at RA-3 Reactor: computational dosimetry and boron biodistribution study

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The lung is the main, if not the only, metastatic site for various tumors. In the advanced disease stage, metastases could be multiple, and for these cases, current treatment is only palliative (chemotherapy protocols) with a prognosis of less than 10% survival at 5 years. Several metastatic diseases are limited to the lung without extrapulmonary invasion (i.e. Oligometastatic disease, Wilm's and Ewing's sarcoma lung metastasis). In this scenario, a BNCT lung ex-situ protocol is a potentially therapeutic strategy. Following the TAOOrMINA procedure applied in Italy to

treat colon metastases in liver, the proposed protocol involves irradiation of the explanted organ while the patient is kept stable at the operating room, followed by the re-implantation of the treated organ. This procedure maximizes the delivered dose to each target independently of their position and/or shape while completely sparing the surrounding organs at risk that are present in the chest cavity. Also, the technique guarantees tissue compatibility between patient and organ and eliminates the need for immunosuppression. A big animal pre-clinical model is proposed as a realistic representation for the assessment of the treatment in patients. Healthy adult sheep are thus being used to study the feasibility of the surgical procedure and healthy lung toxicity derived from whole organ irradiation using the BNCT ex-situ facility at CNEA RA-3 reactor. This work presents the results for the first pre-clinical phase consisting of surgical optimization, BPA biodistribution studies and computational dosimetry.

Surgeons performed 8 surgical procedures to optimize the ablation technique, prosthesis required for re-implantation and period of ischemia. BPA (i.v. 350 mg BPA/kg, 45 min infusion) kinetics was studied in 3 adult sheep. Blood, lung and other relevant tissues were sampled periodically over 5 hours. Given that ex-situ BNCT involves perfusion of the organ with a conservation solution, 2 of the biodistribution studies included perfusion of the organ to determine the effect of this procedure on boron retention. Finally, computational dosimetry was employed to determine the feasibility of treating a human lung. The spatial dosimetry associated to the ex-situ protocol at the RA-3 thermal column central facility was calculated based on radiotolerance constraints and boron concentration data in sheep.

With practice, lung explantation time was reduced from 205 to 85 minutes from the end of BPA infusion. Tailored autotransplant techniques were developed. Analysis of BPA kinetics in the adult sheep revealed that blood and normal tissue boron concentration-time profiles are qualitatively and quantitatively equivalent to those in humans. Moreover, boron concentration is homogenous in the lung volume and the lung-to-blood ratio remains constant at a value of 1.2 from 120 minutes after the start of BPA infusion. After the organ conservation protocol the boron retention factor in lung was 0.5, consistent with observations in a rat model of metastatic lung disease. Based on a human explanted lung CT study and assuming the boron concentration values derived from sheep, a treatment plan was calculated considering 10 randomly distributed nodules. Treatment time to deliver therapeutic doses to the tumors was less than 10 minutes. A very promising average tumor control probability is derived: a mean total control of 82 % is achieved even when a 2.5 tumor-to-normal tissue boron ratio is considered.

These encouraging results from this first pre-clinical phase allowed us to validate our animal model in terms of boron kinetics. Moreover, dosimetric results support the high therapeutic potential of our treatment protocol. Authorizations have been secured for the second phase of this project consisting of the evaluation of healthy lung toxicity following whole organ irradiation. The first ex-situ full procedure is scheduled for April. The follow-up period will extend until the end of June.

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