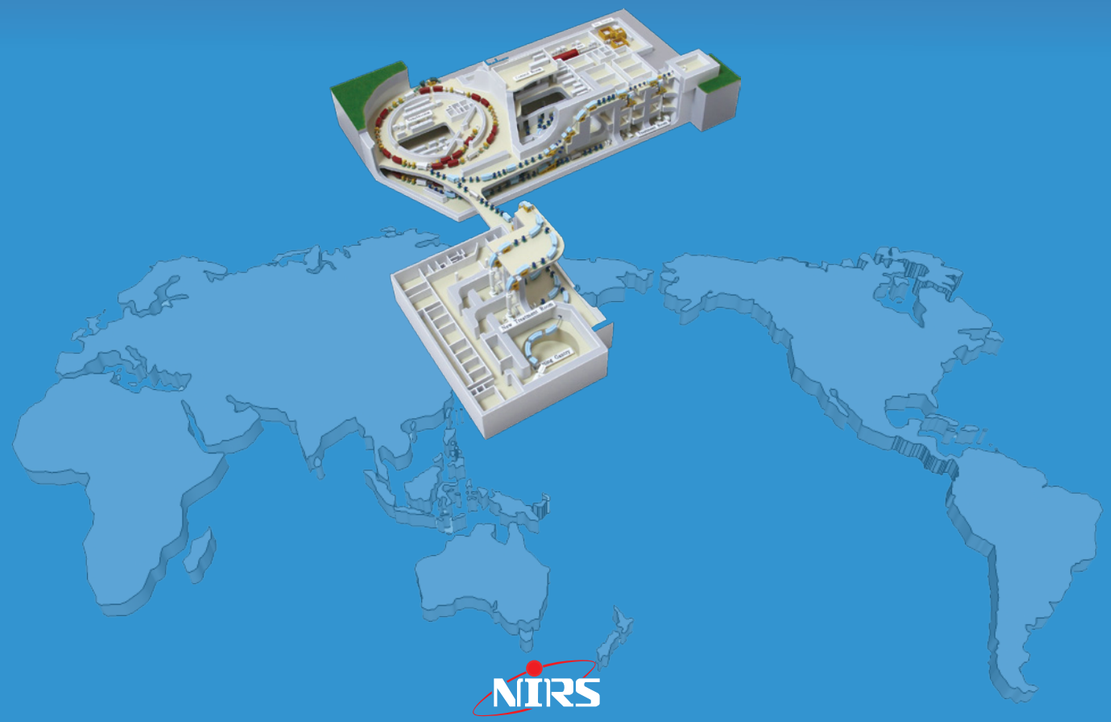
NIRS-M-272

HIMAC
International Symposium 2015

20 -Year Anniversary Event

19-20 January 2015
Akiba Hall, Tokyo, Japan

Abstracts



NIRS-M-272 HIMAC International Symposium 2015

National Institute of Radiological Sciences
HIMAC International Symposium 2015.
4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan
Phone: +81-43-206-3025
Fax: +81-43-206-4061
himac-sympo2015@nirs.go.jp

HIMAC

International Symposium 2015

20-Year Anniversary Event

14th Heavy Ion Charged Particle Therapy Symposium

19-20 January 2014
Akiba Hall, Tokyo, Japan

Abstracts

Organized by:
Research Center for Charged Particle Therapy
National Institute of Radiological Sciences

Preface

I am pleased to welcome you all to HIMAC International Symposium 2015. This symposium has been organized as a special international event to commemorate the 20th anniversary of the initiation of carbon ion radiotherapy at HIMAC of the National Institute of Radiological Sciences (NIRS) in Japan. Since 1994, HIMAC has carried out clinical trials of cancer treatments using carbon ion beams. Having accumulated clinical experience in various types of malignant tumors, NIRS was successful in obtaining approval from the Ministry of Health, Labour and Welfare to carry out carbon ion radiotherapy as a "Highly Advanced Medical Technology" in 2003. Carbon ion radiotherapy has achieved for itself a solid place in the general practice of treating cancer. By the year 2016, the total number of patients will reach 10,000. In addition, NIRS started treatment with scanned carbon ion beams in 2011, working hard toward a more patient-friendly cancer therapy. For this event, we have invited experts in charge of carbon ion radiotherapy facilities both inside and outside Japan, which are either in operation, under construction, or in the planning stage, to introduce the current status and prospects of their facilities or plans. I believe this symposium will serve as a good opportunity for all of us to share the latest information and future prospects, as well as exchange ideas for future development in this field.

Dr. Tadashi Kamada

Director of Research Center for Charged Particle Therapy, NIRS

HIMAC International Symposium 2015

◇ 20-Year Anniversary Event ◇

19-20 January 2015, Akiba Hall, Tokyo, Japan

Mon. 19 January 2015

9:30	- 10:00	(30)	Registration		
10:00	- 10:10	(10)	Opening Remarks	Yoshiharu Yonekura	(NIRS)
10:10	- 10:20	(10)	Congratulatory address	MEXT	
			Outline of Heavy Ion Radiotherapy	**Chair : Robert Miller**	
10:20	- 10:40	(20)	Twenty Years of Carbon Ion Therapy at NIRS, Chiba, Japan	William Chu	(LBNL)
10:40	- 11:00	(20)	Japanese Experience of Carbon Ion Radiotherapy	Hirohiko Tsujii	(NIRS)
11:00	- 11:10	(10)	*Q&A*		
			Future Prospects (1)	**Chair : Tadashi Kamada**	
11:10	- 11:25	(15)	Particle Therapy Project at UTSW and P20	Hak Choy	(Univ. Texas SW)
11:25	- 11:40	(15)	The UCSF P20 and the Development of a Heavy Particle Radiotherapy (HPRT) Program	Mack Roach	(Univ. California SF)
11:40	- 11:55	(15)	The Mayo Clinic Vision for Heavy Charged Particle Therapy	Robert Miller	(Mayo Clinic)
11:55	- 12:10	(15)	Sustainable Business Using Next-Generation Technology	Keishin Sasaki	(Keio Univ.)
12:10	- 12:25	(15)	*Q&A*		
12:25	- 14:00	(95)	*Lunch Break*		
			Clinical Experience at the Present Facilities (1)	**Chair : Ramona Mayer**	
14:00	- 14:15	(15)	Clinical Experience of Carbon Ion Radiotherapy at GSI/Heidelberg	Stefan Rieken	(HIT)
14:15	- 14:30	(15	Clinical Experience of Carbon Ion Radiotherapy at IMP	Guoqing Xiao	(IMP)
14:30	- 14:45	(15)	Current Status of Carbon Ion Therapy for Cancers at GHMC	Takashi Nakano	(GHMC)
14:45	- 15:00	(15)	*Q&A*		
			Clinical Experience at NIRS	**Chair : Kenji Nemoto**	
15:00	- 15:40	(40)	Overview of Clinical Results on Carbon Ion Radiotherapy at NIRS	Tadashi Kamada	(NIRS)
15:40	- 15:50	(10)	*Q&A*		
15:50	- 16:10	(20)	*Break*		
			Radiation Biology	**Chair : Jac Nickoloff**	
16:10	- 16:25	(15)	Review of Biology Related to Heavy-Ion Radiotherapy	Eleanor Blakely	(LBNL)
16:25	- 16:40	(15)	Recent Progress of Particle Radiation Biology	Marco Durante	(GSI)
16:40	- 16:55	(15)	DNA Repair and Checkpoint Pathways in Human Cells Exposed to Heavy Ion Radiation	Hirohiko Yajima	(NIRS)
16:55	- 17:10	(15)	The Combination of Carbon-Ion Radiotherapy and Immunotherapy in *In Vivo* Mouse Models	Takashi Imai	(NIRS)
17:10	- 17:25	(15)	*Q&A*		

Tue. 20 January 2015

			Clinical Experience at the Present Facilities (2)	**Chair : Yuko Nakayama**	
9:30 -	9:45 (15)	Clinical Activities at the Italian National Center for Oncologic Hadrontherapy CNAO	Roberto Orecchia	(CNAO)
9:45 -	10:00 (15)	Clinical Experience of SAGA HIMAT	Sho Kudo	(SAGA HIMAT)
10:00 -	10:15 (15)	Proton and Carbon Irradiation in Shanghai Proton and Heavy Ion Center	Guoliang Jiang	(SPHIC)
10:15 -	10:30 (15)	Which of the Two Particle Therapies (Carbon Ions and Protons) is Better in Cancer Treatment?	Nobukazu Fuwa	(HIBMC)
10:30 -	10:45 (15)	*Q&A*		
10:45 -	11:15 (30)	*Break*		
			Status of Facilities under Construction	**Chair : Takashi Nakano**	
11:15 -	11:30 (15)	Current Status of MedAustron	Ramona Mayer	(Med Austron)
11:30 -	11:45 (15)	Current Status of i-ROCK (Kanagawa)	Yuko Nakayama	(Kanagawa Cancer C.)
11:45 -	12:00 (15)	Current Status of KHIMA Project	Chul-Koo Cho	(KIRAMS)
12:00 -	12:15 (15)	*Q&A*		
12:15 -	13:45 (90)	*Lunch Break*		
			Future Prospects (2)	**Chair : Hak Choy**	
13:45 -	14:00 (15)	Particle Radiotherapy from NCI Point of View	Bhadrsain Vikram	(NCI, NIH)
14:00 -	14:15 (15)	Planning for a Heavy Ion Radiotherapy Research and Treatment Center in Colorado	Jac Nickoloff	(Colorado State Univ.)
14:15 -	14:30 (15)	Heavy Ion Radiotherapy Project at Yamagata University Hospital	Kenji Nemoto	(Yamagata Univ.)
14:30 -	14:45 (15)	Future Plans for Carbon Ion Radiotherapy in Okinawa	Takafumi Toita	(Ryukyu Univ.)
14:45 -	15:00 (15)	*Q&A*		
15:00 -	15:30 (30)	*Break*		
			Hardware Development and Medical Physics	**Chair : William Chu**	
15:30 -	15:45 (15)	Recent Status of HIMAC R&D for Next Generation	Koji Noda	(NIRS)
15:45 -	16:00 (15)	Development on Rotating Gantry with Superconducting Magnets	Toshiyuki Shirai	(NIRS)
16:00 -	16:15 (15)	Recent Status of GSI/Heidelberg R&D for Next Generation	Thomas Haberer	(HIT)
16:15 -	16:30 (15)	Status of Biological Treatment Planning at HIT with The Local Effect Model (LEM)	Oliver Jäkel	(DKFZ)
16:30 -	16:45 (15)	Biological Models for Carbon-Ion Radiotherapy at NIRS	Naruhiro Matsufuji	(NIRS)
16:45 -	17:00 (15)	*Q&A*		
17:00 -	17:05 (5)	**Closing Remarks**	Tadashi Kamada	(NIRS)

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Status of Facilities under Construction

Future Prospects (2)

Hardware Developments and Medical Physics

Day 1

Twenty Years of Carbon Ion Therapy at NIRS, Chiba, Japan

William T. Chu

EO Lawrence Berkeley National Laboratory, Berkeley, California, USA
E-mail: wtchu@LBL.gov

In 1938, Ernest Orlando Lawrence built the 184-Inch Synchrocyclotron in his Radiation Laboratory in Berkeley, California, accelerating protons and heavier ions to the energies never attained before. Robert R. Wilson, one of his graduate students, realized that the penetrating proton and heavier ion beams could be utilized to treat deep-seated tumors in humans[#]. Soon after, at the EO Lawrence Berkeley National Laboratory (LBNL), exploratory clinical trials were conducted, followed by full-fledged clinical trials (1975-1992) to treat approximately 1000 patients primarily with helium and neon ions. In 1994 in Japan, the National Institute of Radiological Sciences (NIRS) commissioned the first-in-the-world medical use-dedicated Heavy Ion Medical Accelerator in Chiba (HIMAC), which accelerates several species of heavy ions up to an energy of 800 MeV/μ (Million electron Volts per nucleon). The HIMAC's early operations demonstrated the clincal efficacy of carbon ions to treat malignant tumors in patients relying on the unique radiobiological properties of densely ionizing radiation. Encouraged by successful clinical results, several carbon-ion therapy facilities have since been constructed and commissioned around the world: at Hyogo (commissioned in 2001), Gunma (2010), Toshu (2013), and Kanagawa (2014) in Japan; Heidelberg (2009) and Marburg (2015) in Germany; Pavia (2010) in Italy; Lanzhou (2009) and Shanghai (2014) in China; and Wiener Neustadt (2015) in Austria. We look forward to the construction and commisssioning of carbon-ion therapy facilities currently in planning stages to enlarge globally the capacity of valuable clinical modalities. As we enter the third decade since the inauguration of HIMAC, carbon-ion therapy centers around the world envisage an exciting future with increasingly extensive collaborative and comparative clinical trials. These centers promise to accelerate scientific and technological progress, enhancing the clinical efficacy of future ion-beam therapy by, for example, studying robust radiobiological understandings that enable rational designs of clinical trials and their intercomparisons, and improving beam delivery accuracy through patient-friendly beam scanning that compensates for organ movements. At the twentieth anniversay of the HIMAC operaton, we laud the farsighted investment and numerous innovations of NIRS that launched carbon ion therapy into the forefront of cutting-edge technology in radiation cancer treatment.

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* This work was supported by the Director, Office of Science of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

[#] R. R. Wilson, "Radiological Use of Fast Protons," *Radiology*, **47**:487-491 (1946).

Japanese Experience of Carbon-Ion Radiotherapy

Hirohiko Tsujii

National Institute of Radiological Sciences, Chiba, Japan

E-mail: tsujii@nirs.go.jp

Rationale for using carbon-ions for cancer therapy lies primarily on improved dose distribution and radiobiological characteristics of high-LET radiations, permitting the potential modification of treatment efficacy to increase the differential in the biological response of tumor and the surrounding normal tissues. At present, there are 7 carbon-ion therapy facilities in operation in the world, in which more than 100,000 patients have been treated with >80% of them being treated at NIRS, Japan. Through clinical experiences of NIRS and GSI, photon-resistant tumors have been successfully treated and a significant reduction in overall treatment time has been achieved. There are currently 4 facilities in operation and one under construction in Japan. As of early 2014, approximately 8,000 patients are treated at NIRS, >1,000 patients at Gunma University and >400 patients at SAGA-HIMAT. At Hyogo facility, a total of 5,381 patients were treated from 2001 to 2012 with 69% for protons and 31% for carbon-ions.

NIRS started clinical trials in 1994 to evaluate the clinical efficacy of carbon-ions generated from the HIMAC. Since then, trials have been carried out to determine the tumor types that can be effectively treated with carbon-ions, to identify the optimum dose-fractionation patterns, and to develop irradiation techniques for precise delivery of carbon-ions. The experiences to date indicate that C-ion RT is advantageous for the tumors that are generally photon-resistant and those located in the vicinity of critical organs. These include skull base tumors, head and neck cancer, NSCLC, HCC, pancreatic cancer, prostate cancer, post-operative recurrence of rectal cancer, bone/soft tissue sarcoma, and uterine cervix adenocarcinoma. However, if the tumor infiltrates or originates in the digestive tract, it was difficult to control them with C-ions. A significant reduction in fractions and treatment time has been achieved with acceptable toxicities in most cases. For example, stage I lung cancer and liver cancer can be treated with only one or two fractions, respectively. Even for prostate cancers, 12 fractions in three weeks have been sufficient.

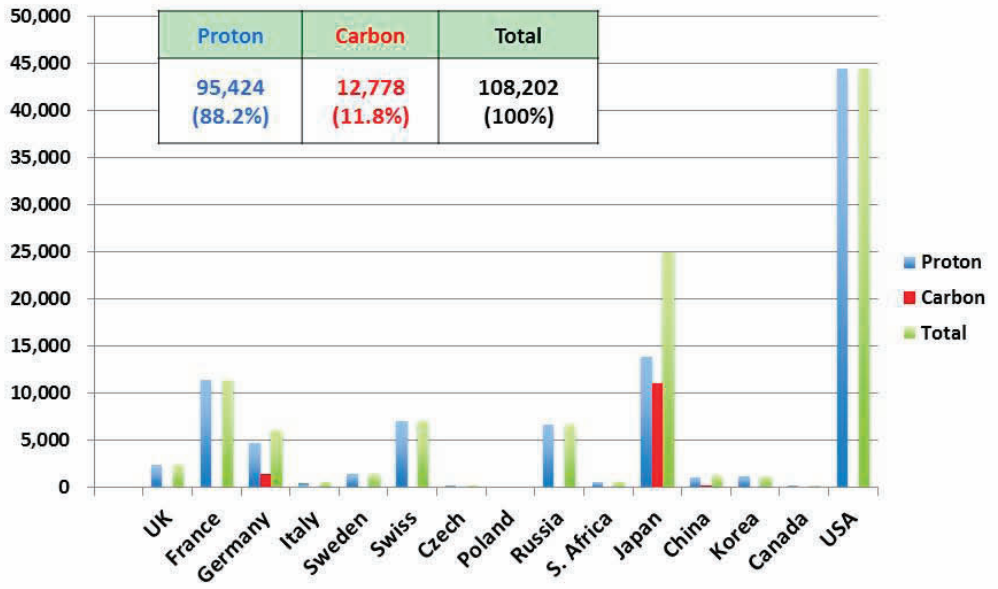
In 2010 a new facility was built with the beam lines being extended from the HIMAC accelerators. In this facility, we started treatment with a pencil beam scanning in 2011, and its indications have been expanded to many types of tumors. Pencil beam scanning will soon become available for treatment of a moving target. With this technique, we will be able to further shorten the treatment course.

Carbon Facilities in Operation in the world

Institute /Hospital	Location (Country)	Vendors	Period	Treatment rooms	Irradiation method	Max. Energy MeV/u
HIMAC	Chiba (Japan)	4 companies	1994~	3+3	Wobbler Layer stacking Scanning	400(C)
HIBMC	Hyogo (Japan)	Mitsubishi	2001~	2+3	Wobbler	320(C) 230(p)
IMP	Lanzhou (China)	IMP	2006~	2	Wobbler Layer stacking	100 for V 400 for H
HIT	Heidelberg (Germany)	Siemens*	2009~	3	Scanning	430(C) 250(P)
GHMC	Gunma (Japan)	Mitsubishi	2010~	3	Wobbler Layer stacking	400(C)
CNAO	Pavia (Italy)	CERN+CNAO	P: 2011~ (C: 2012)	3	Scanning	400(C) 250(P)
SAGA-HIMAT	Saga (Japan)	Mitsubishi	2013~	3	Wobbler (Scanning)	400(C)
SPHIC	Shanghai (China)	Siemens*	2014~	4	Scanning	430(C) 221(P)

*** Withdrawals from the business**

Number of patients treated with Protons and C-ions in the world



Taken from PTCOG (As of 26-June-2014)

Particle Therapy Project at UTSW and P20

Hak Choy

National Particle Therapy Research Center (NPTRC)
Texas Center for Advanced Radiation Therapy (TCART)
Dallas Texas USA
E-mail: Hak.Choy@UTSouthwestern.edu

Photons, protons, or ^{12}C nuclei have all been effectively utilized as radiotherapy for cancer. However, the number of individuals worldwide who have been treated with charged particles is relatively small (108,000), with only about 11,000 treated with ^{12}C. As a result and despite their identified strengths, there are still numerous open questions and concerns that should be addressed before particle beam radiation therapy (PBRT) is fully implemented in cancer care. Substantial pre-clinical, clinical, physics, socio-economic and cost benefit research is needed.

In 2013, UT Southwestern created a master plan to establish the National Particle Therapy Research Center (NPTRC) which will be affiliated with the final phase, i.e., the ^{12}C therapy facility, of the Texas Center for Advanced Radiation Therapy (TCART). The vision of the NPTRC, and particularly how it integrates with the PBRT facility, requires consideration into the optimal structure, layout, infrastructure, and physical and operating configurations. With the creation of the NPTRC, researchers from across the nation can use the resources to conduct research organized at the national level: in particle and medical physics aimed at the clinical use of charged particles; in radiobiology to better understand the underlying biological mechanisms of tumor and normal tissue response; and in testing the efficacy of PBRT through human clinical trials.

During the next few years of planning stage of NPTRC, we will focus on 1) the identification of the research directions, 2) the development of the research beam line specifications, 3) the recruitment of the relevant expertise needed, 4) the development of research collaborations and consortia, and 5) the development of common platforms for collaborative research.

This University of Texas Southwestern ranks among the top academic medical centers in the world has a long history of demonstrated success in the management of large nationally-recognized research projects, in both the basic research and clinical areas. Our research programs have been funded by NIH, NASA, DOD, and other federal agencies, as well as the Howard Hughes Medical Institute and other major private philanthropies. UT Southwestern also garner significant funding from the state of Texas for our academic mission. Our institution's extensive administrative, research and clinical infrastructure is well suited in building the Texas Center for Advanced Radiation Therapy (TCART) in Dallas, Texas. This one of the most important project not just for our cancer patients but for many cancer patients here in US and abroad.

The UCSF P20 and the Development of a Heavy Particle Radiotherapy (HPRT) Program

Mack Roach III

Department of Radiation Oncology, University of California San Francisco, USA
E-mail: mroach@radonc.ucsf.edu

In 1975 the LBNL and the University of California, San Francisco (UCSF) conducted a series of studies using heavy ions including helium and neon beams for the treatment of several solid tumors (see [1]). Follow-up of these patients ended shortly after 1993 with the budget-forced closure of the clinical facility at LBNL [2]. Our initial experience, after treating more than 2000 patients with light ions at Lawrence Berkeley National Laboratory (LBNL), taught us that only randomized trials can answer the key questions surrounding the value of HRT. Recognizing this problem, the NCI released this FOA that encourages planning efforts for research centers in conjunction with an independent commitment to construct Particle Beam Radiation Therapy (PBRT) facility in the U.S. In response, to this announcement, the North American Particle Therapy Alliance (NAPTA) has been formed. NAPTA brings together experts in radiation oncology, medical and accelerator physics, magnet design, and radiobiology with international consultants from the ion beam facilities in Germany, Italy, and Japan. NAPTA's initial primary focus, to be funded by the P20 grant, will be to build the infrastructure needed to facilitate research in optimizing PBRT delivery and clinical trial design. The long-term goal of NAPTA is to perform clinically relevant research using protons and other light ions up to neon. During the 2-year funding period, we will bring together expertise, existing equipment, and treatment planning software to explore how we can best enable rigorous clinical testing of the *null hypothesis* that incorporation of high-LET ions into PBRT results in no radiobiological/clinical advantage compared to protons alone or photon-based radiation therapy. This can only be accomplished with large-scale randomized clinical trials. Before these trials are launched however we must address technical challenges to accurate delivery of optimized image-guided PBRT. Next, depending on the number of sites that have ions, protons and/or advanced-technology photon capability (including IGRT, IMRT, and SBRT), we will initiate a series of access-weighted Phase III trials.

Specific Aim 1: *Transform existing groups and institutions with clinical interest and/or currently performing R&D work in PBRT into a network of functional teams with a common vision for R&D and clinical studies involving PBRT. Provide the organizational structure within NAPTA to synergistically align these teams.*

Specific Aim 2: *Complete a **Pilot Project** showing how we can move the field forward in addressing issues related to range uncertainty and while integrating the development of "new knowledge" in radiobiology related to how this uncertainty impacts RBE and treatment planning for assessing biological dose distributions.*

Specific Aim 3: *Begin planning for the next two major phases to follow:*

a) Facilitate the development of new, low-cost, compact/efficient designs, for ion accelerators, ion gantries, treatment planning systems, and imaging technology in the treatment room for adaptive planning and QA/verification. Starting with Protons initially at UCSF to be followed by other ions (see description below).

b) Developing the research infrastructure for treating patients with common protocols shared by partner institutions and common technology in the U.S. in synergy with efforts in Europe and Japan.

References:

1. Raju, M.R., *Radiobiologic properties of pions and heavy ions. A comparison.* J Can Assoc Radiol, 1980. **31**(1): p. 26-9.
2. Castro, J.R., et al., *Experience in charged particle irradiation of tumors of the skull base: 1977-1992.* International journal of radiation oncology, biology, physics, 1994. **29**(4): p. 647-55.

The Mayo Clinic Vision for Heavy Charged Particle Therapy

Robert C. Miller
Department of Radiation Oncology, Mayo Clinic, USA
E-mail: Miller.robert@mayo.edu

Most radiotherapy in the United States is delivered through linear accelerator capable of producing high energy photons and through radioisotope delivering brachytherapy. Proton therapy is growing in application in the U.S. and elsewhere, but it is utilized in under 1% of patients in the U.S. Based on pioneering work at the HIMAC in Japan, carbon ion radiotherapy has been demonstrated to be efficacious in the treatment of a number of rare tumors intractable to conventional therapies– sinonasal melanomas, chordomas, chondrosaromas, and other tumor histologies resistant to x-ray and proton radiotherapy.

Charged particles, when used in the treatment of cancer, have both physical and biological advantages over photon therapy. Proton beams leverage the characteristics of the Bragg Peak to allow for more precise dose distribution in comparison to photon beams. Carbon ion radiotherapy has the physical advantages of proton radiotherapy through its sharp Bragg Peak. However, carbon ion radiotherapy also can exploit the unique biological properties of heavier charged particles through its unique action on tumor DNA, allowing for effective cell killing in tumors

The Mayo Clinic Light Ion Particle Radiotherapy Center will be a national resource for the treatment of radio-resistant tumors. This facility will provide confirmatory data on the efficacy of light ion therapy in the treatment of malignant histologies where carbon ions have demonstrated initial promise in Japan and Germany. The targeted histologies in the U.S. facility will be those which are radio-resistant due to tumor histology, hypoxia, and/or other biological factors. We envision treating tumors with a high risk of local failure if treated with conventional photon and proton radiotherapy where there are also no effective surgical or systemic options. Primary clinical indications of interest will be rare tumors refractory to conventional therapies such mucosal melanomas, adenoid cystic carcinomas, chondrosarcomas, chordomas, and other histological types identified as potential candidates for ion therapies. Additionally, tumor types such as glioblastoma, pancreatic cancer, and lung cancers where initial Phase I/II trials at NIRS in Japan have shown promise will be considered for clinical trials aimed at clarifying the roles of carbon ions in their treatment. The center will have a capacity of 750 to 1,000 patients treated per year. The carbon ion facility would be operated in conjunction with our existing proton and photon radiotherapy practices The Mayo Clinic Cancer Center has a robust infrastructure base for clinical trial design and execution as well as translational science. The Mayo Clinic Center for the Science of Healthcare Delivery has partnered with the proton beam radiotherapy program in comparative effectiveness research and will continue to do so in our carbon ion radiotherapy program.

Sustainable Business Using Next-Generation Technology

Keishin Sasaki

Graduate School of System Design and Management, Keio University, Yokohama, Japan
E-mail: keishin.sasaki@sdm.keio.ac.jp

Due to the enormous initial investment, it has been difficult to establish a sustainable business with heavy ion therapy. In this talk we will consider scenarios that make use of “next-generation heavy ion technologies” to improve profitability, thus making a sustainable business operation feasible.

Particle therapy is considered effective for ① refractory cancers, ② cancers with significant side-effects, and for satisfying ③ QOL demands. For proton therapy, however, there have been changes in the insurance reimbursement in the USA because the difference in the clinical outcomes in comparison to conventional radiation treatments is not clear, creating a difficult situation for hospital management. The large number of treatment sessions (time) is also a burden on the patients.

Compared to the proton beam, heavy ion beam systems may offer a superior potential from both the clinical and the business perspectives because (a) the range of treatable site is wider, and (b) the treatment times are shorter, improving patient throughput. Nevertheless, using the conventional heavy ion beam technologies, patient throughput may not meet expectations, and there is a strong possibility that the balance of payments will be negative. By introducing “next-generation heavy ion technologies” the increased patient throughput and expanded range of application can help achieve profitable operation, allowing a sustainable business to be established.

Clinical Experience of Carbon Ion Radiotherapy at GSI/Heidelberg

Stefan Rieken*, Jürgen Debus

Department of Radiation Oncology, University Hospital Heidelberg, Germany
*E-mail: Stefan.rieken@med.uni-heidelberg.de

Introduction

The clinical use of heavy ions in the context of modern radiotherapy looks back on more than 15 years of experiences at the University of Heidelberg. In 2014, more than 700 patients were treated. Innovations such as the use of the ion gantry, regular PET-assisted positioning controls and multimodality treatment concepts with sequential photon irradiation and simultaneous administration of chemotherapies have been introduced to improve patient care.

Results

More than 2000 patients have been treated at HIT since the mid 90s. Treatment-associated toxicities are moderate. For patients with chordomas and chrondrosarcomas, particle irradiation with carbon ions has gained wide acceptance and has become a new standard of care reaching local control rates ranging from 60 to 90 % after 10 years. Promising clinical studies are now open to investigate the benefit of particle irradiation for patients with prostate, rectal and lung cancer, and with central nervous system tumors.

The gantry has opened up new possibilities for beam arrangements that allow excellent coverage of targets with simultaneous sparing of organs at risk.

Preclinical investigations of the biological effects of particle irradiation have brought up interesting combinations of carbon ion irradiation with chemotherapy and have also addressed the role of oxygen ions in clinical routine.

Conclusion

Particle radiotherapy is fully integrated into daily clinical routine and has yielded excellent clinical results for over 2000 patients in Heidelberg. The use of particles in modern radiotherapy concepts will increase continuously and is likely to replace photons as the standard modality in many fields of radiation oncology.

Clinical Outcome and Recent Progress of Heavy Ion Radiotherapy at IMP

Guoqing Xiao*, Hong Zhang, Qiang Li

Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou, China
*E-mail: xiaogq@impcas.ac.cn

Based on the heavy ion accelerators available at the Institute of Modern Physics (IMP), Chinese Academy of Sciences, clinical trial of heavy ion radiotherapy has gotten started at IMP in collaboration with local hospitals since 2006. Up to now, 213 tumor patients including 103 superficially-placed and 110 deep-seated tumor patients have been treated with carbon ions at IMP. Preliminary clinical results showed all the tumors responded well to the treatment and significant curative effect has been obtained. In the patient followup, no severe side effects have been observed to date. In this talk, the clinical outcome of heavy ion radiotherapy achieved at IMP will be reported. Besides, two dedicated heavy ion therapy facilities, which are technically supported by IMP, are now under construction in Lanzhou and Wuwei, China. The most compact design of synchrotron in the world as the main accelerator with circumference of 56.17m is adopted in the dedicated therapy facilities. Recent progress of the dedicated heavy ion therapy facilities will be introduced in this talk as well.

Current Status of Carbon Ion Therapy for Cancers at GHMC

Takashi Nakano

Gunma Heavy Ion Medical Research Center
Radiation Oncology, Graduate School of Medicine, Gunma University, Japan
E-mail: tnakano@med.gunma-u.ac.jp

Heavy ion radiotherapy has been spotlighted not only in superior dose convergence but also the high biological effectiveness and is one of the minimally invasive treatments that gives best QOL after treatment in addition to a strong ability to control cancer. The heavy ion therapy will become an important radiation therapy for cancer in the near future.

The heavy ion therapy is a treatment that ions such as carbon ions are accelerated to nearly 70 percent of the speed of light and are used for cancer treatment. The heavy ions have two major characteristics that they have excellent dose-distribution superior to X-rays therefore can treat the tumor more selectively and, another one, have 2-3 times stronger cell killing power than X-rays and protons therefore can effectively control the radiation-resistant tumors such as liver cancer, malignant melanoma, bone and soft tissue sarcoma and other adeno-carcinoma cell types. In addition, hypofractionation / short term treatment method is effective so that patient lord is significantly slight.

According to treatment results of clinical trials of carbon ion beam therapy for over 8000 patients, which was started in June 1994 in the NRIS in Chiba Japan, at present, lung cancer, liver cancer, head and neck cancer, prostate cancer, bone and soft tissue sarcoma and so on are considered good choices for heavy ion therapy.

The Gunma University started heavy ion therapy with the development of concise heavy ion therapy facility from March 2010 and more than 1000 patients with various cancers have been treated safely. Most of the patients were treated with hypofractionated regimens, for example, 4 fractions over 4 days for lung cancers and liver cancers. The present paper introduces present status of the heavy ion therapy quoted with results at NIRS with adding our recent clinical outcome and outline of Gunma heavy ion therapy project including technological development of a high–precision carbon ion micro-surgery system which create small beam spot of 1-3mm in diameter with a highly precise spatial position less than a millimeter. This treatment technique can extend the application for benign diseases other than cancers for future.

In particular for clinical results among the phase II clinical trial at GHMC, the clinical trial of lung cancer (GUNMA0701) which was performed for 34 lung cancer patients of inoperable / refusal of operation treatment from June 2010 to June showed the treatment results of two-year local control, the cause specific survival, and the overall survival rates were 94%, 95%, and 91%, respectively. Regarding the adverse event of the lung, one Grade 2 and one Grade 3 complication in the lung were observed for patients with atypical mycobacterial disease and pulmonary emphysema, respectively. This is the similar to that of the treatment results of National Institute of Radiological Sciences, and is considered to be similar to those for the patients with surgical treatment. Moreover, in the clinical trial of prostatic cancer (GUNMA0702), 306 patients were treated from June 2010 to July 2013, and the two-year local control rate and the biochemical relapse-free rate were 100% and 98.4%, respectively. Regarding the late complication rates of Grade 2 were 0.3% of the rectum. 3.9% of the urinary tract and no people for Grade 3 and greater, which are fewer in compared with the other results of X ray treatment and proton radiotherapy.

Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas

Tadashi Kamada

Research Center for Charged Particle Therapy
National Institute of Radiological Sciences, Chiba, Japan
E-mail: t_kamada@nirs.go.jp

As a high linear energy transfer charged particle beam, carbon ion beam has been expected to be an effective and safer treatment for radio-resistant sarcomas. NIRS conducted a dose searching clinical trial using carbon ion beam on the unresectable bone and soft tissue sarcomas. Between June 1996 and February 2000, fifty seven patients with unresectable bone and soft tissue sarcomas were enrolled in the study. This study produced a favorable tumor control rate of 63% at 3 years. The overall survival rates were 82% at 1 year, 47% at 3 years, and 37% at 5 years, respectively. The median survival was 31 months. There was a significant difference in the results for the local control rate achieved with a total dose of 57.6GyE or less and that with 64.0GyE or more. As 7 of the 17 patients treated with 73.6GyE were found to have Grade 3 RTOG acute reactions in the skin, the dose escalation was halted at this dose level. These findings made it clear that with a dose fractionation regimen of 16 fractions over 4 weeks, a total dose of 70.4GyE was the maximum applicable dose in patients for whom there was sufficient skin close to the tumor, while a total dose of 73.6GyE was possible in other cases. In the subsequent phase II study started in April 2000, 622 candidates (641 sarcomas) have been enrolled as of August 2014. The 620 lesions of 601 patients treated with carbon ion beam followed for six months or longer were analyzed. The prescribed dose of 73.6GyE (4.6GyE /fraction) was applied in the phase I and phase II clinical trial, however it has been closed due to relatively high incidence of grade >3 acute and late skin reactions in the patients deceiving this dose level during the early phase II study. As of August 2014, the 2-year and 5-year local control rates were 84% and 68%, respectively. The two–year and 5-year overall survival rates were 80 % and 59%, respectively. The toxicity was acceptable level at 2% skin/soft tissue late G3/4 toxicity so far. Carbon ion radiotherapy is an effective and safe treatment for patients for whom surgical resection is not a viable option, and it seems to represent a promising alternative to surgery.

Skull Base / Head & Neck

Masashi Koto[1*], Ryo Takagi[1], Hiroaki Ikawa[1], Kensuke Naganawa[1]
[1]Research Center for Charged Particle Therapy
National Institute of Radiological Sciences, Chiba, Japan
[*] E-mail: koto@nirs.go.jp

Introduction: Head and neck malignancies include malignant tumors of various histologies. Squamous cell carcinomas (SCCs) which account for the majority of these tumors are radio-sensitive, however, most non-SCCs are both radio- and chemo-resistant. Therefore, achieving local control remains a challenge in patients with inoperable non-SCCs.

The management of skull base tumors is challenging, because they lie in close proximity to critical structures such as the brainstem, spinal cord and anterior optic pathways. These anatomical structures often limit surgical access and resectability, as well as the delivery of high-dose radiations.

As compared with photons, carbon ions offer a biological advantage because they have higher linear energy transfer components in the Bragg peak. Carbon ions also offer a higher degree of physical selectivity because they have a finite range in tissue. Therefore, carbon ion therapy permits better dose conformity than can be obtained with photon therapy. Consequently, carbon ion therapy can potentially control radio-resistant tumors while sparing normal tissues.

Protocols & Results: More than 800 locally advanced tumors were treated in head and neck protocols with 16 fractions over four weeks, with total doses of 64.0 Gy equivalent (Gy E) or 57.6 Gy E. The treatment results obtained so far indicate that a favorable 5-year local control rate of around 70-80% has been achieved, mainly for adenoid cystic carcinoma, adenocarcinoma, and mucosal malignant melanoma. With regard to sarcomas arising from the head and neck region, a total dose was escalated to 70.4 Gy E in 16 fractions to obtain a sufficient local control rate. Mucosal malignant melanoma is treated with a combined regimen using carbon ion therapy and chemotherapy in order to control or prevent distant metastasis.

Skull base tumors such as chordoma and chondrosarcoma are treated with a total dose of 60.8 Gy E in 16 fractions. The 5-year local control rate is around 80% with acceptable toxicities.

Conclusion: Carbon ion therapy has been performed for radio-resistant tumors in the head & neck and skull base regions, demonstrating excellent clinical results.

Treatment protocols by tumor histologies

Histology	Protocol
Carcinoma	64.0 Gy E or 57.6 GyE/16 frs.
Mucosal malignant melanoma	64.0 Gy E or 57.6 GyE/16 frs. + Chemotherapy
Sarcoma (except low grade chondrosarcoma)	70.4 Gy E/16 frs.
Skull base tumor (chordoma etc.)	60.8 Gy E/16 frs.

Hypofractionated Carbon Ion Therapy of Lung Cancer

Naoyoshi Yamamoto

Research Center for Charged Particle Therapy
National Institute of Radiological Sciences, Chiba, Japan
E-mail: nao_y@nirs.go.jp

Introduction

In 1994, we began using carbon-ion radiotherapy (CIRT) for the treatment of peripheral stage I non-small cell lung cancer (NSCLC). Between 1994 and 1999, a phase I/II dose escalation study of the treatment of stage I peripheral NSCLC was conducted to determine the optimal dose of therapy and evaluate whether progressing to hypofractionated CIRT was feasible. Another purpose of these trials was to develop precise and safe irradiation techniques with maximum sparing of normal tissue. Two phase I/II clinical trials demonstrated the optimal doses of 90.0 GyE in 18 fractions over six weeks (Protocol #9303) and 72.0 GyE in nine fractions over three weeks (Protocol #9701) for achieving more than 95% local control with minimal pulmonary toxicity.

As a next step, we conducted two successive phase II trials. The first trial (Protocol #9802) used a regimen of 72 GyE in nine fractions over three weeks, and the second trial (Protocol #0001) used a regimen of four fractions over one week at a fixed dose of 52.8 GyE for stage IA patients and 60 GyE for stage IB patients. In these phase II trials, the local control rate (LCR) for all patients was 91.5%, while that for patients with T1 and T2 tumors was 96.3% and 84.7%, respectively. The 5-year overall survival (OS) rate was 45.3% (IA: 53.9, 1B: 34.2). No adverse events greater than grade 2 occurred in the lungs.

In 2003, we initiated a phase I/II clinical trial (Protocol #0201) as a dose escalation study using a single fraction. The initial total dose was 28.0 GyE administered and escalated in increments of 2.0 GyE each, up to 50.0 GyE. That clinical trial ended in February 2012 and remains in follow-up. In this article, we investigated the preliminary results of this phase I/II trial.

Materials and Methods

In this prospective study, 151 primary stage I NSCLC patients were treated with CIRT monotherapy with a total dose of 36.0 GyE or more using single fractionation. The mean patient age was 73.9 years, and the tumors included T1 (n=91) and T2 (n=60) lesions. According to type (the cancer type was determined via biopsy), there were 104 adenocarcinomas, 46 squamous cell carcinomas and one large-cell carcinoma. The rate of medical inoperability was 55.6%.

Results

The median follow-up time was 47.9 months (range, 1.6-105.9 months). Among the 151 patients who received 36.0 GyE or more, the 5-year LCR was 79.2%, while that for the patients with T1 (n=91) and T2 (n=60) tumors were 84.5% and 70.9%, respectively. The 5-year OS was 55.6%. Furthermore, the result of 20 patients who received 48 or 50 GyE were better, the 2-year LCR and OS were both 95%.No toxicities greater than grade 2 were observed in the lungs or skin.

Conclusions

In patients with stage I NSCLC, CIRT using a single fraction is considered to be a promising curative modality.

Carbon Ion Radiotherapy for Stage I Breast Cancer

Kumiko Karasawa*, Tokuhiko Omatsu, Tadashi Kamada

Research Center Hospital for Charged Particle Therapy
National Institute of Radiological Sciences, Chiba, Japan
*E-mail: kkarasaw@nirs.go.jp

Carbon ion radiotherapy (C-ion RT) considered suitable for meeting the aim of lessening the treatment burden in early cancer by taking advantage of the better dose distribution and high biological effectiveness. Our institute started a clinical trial of C-ion RT for patients with low risk T1N0M0 invasive ductal carcinoma in 2013. The purpose of this presentation is to evaluate the preliminary effectiveness and usefulness of C-ion RT for low risk stage I breast cancer.

A candidate of C-ion RT for breast tumor is T1N0M0, postmenopausal, ER positive, HER2 negative, invasive ductal carcinoma or other favorable type, without extensive intra-ductal component, without lymph vascular space invasion, and tumor located more than 5 mm from the skin. Tumor extension including ductal spread has to be evaluated by enhanced MRI before treatment decision. Two fiducial markers (Visicoil^{TM}; IBA) are implanted for position collation. Clinical target volume (CTV) is defined as the gross tumor and intraductal component detected by MRI images. Safety margins of 5 mm and an anterior margin of 5 mm are added to CTV to create the initial planning target volume (PTV) excluding the region within 5 mm from skin surface. Three-field C-ion beams with 290 MeV/n energy are used by means of passive broad beam methods. Irradiation is performed using respiratory gating. Treatment duration is one week, daily from Tuesday to Friday.

In phase I clinical trial for determining recommended dose, tumor resection is performed 3 months after the treatment for observing pathological effects. The dose levels are 48.0 GyE, 52.8 GyE and 60.0 GyE in 4 fractions within one week, respectively. In phase II, treatment outcome observes without surgery after the recommended dose treatment. For patients who do not wish to participate in a clinical trial, C-ion RT was performed as advanced medicine.

From April 2013 to December 2014, 14 cases were treated. Patient' age ranged from 44 to 81 with a median of 66. The tumor sizes were 4 to 20 mm with a median of 12 mm. The radiation doses were 48GyE in 3, 52.8GyE in 6 and 60.0GyE in 5. The follow up period ranged from 1 month to 19 months with a median of 5 months. No acute adverse toxicities have been observed except for grade 1 skin reaction in 5 cases. At the time of analysis, 2 patients reached pathological CR and 2 patients reached clinical CR.

Clinical investigation of C-ion RT for patients with low risk T1N0M0 invasive ductal carcinoma is safe and worth to continue.

Carbon Ion Radiotherapy for Hepatocellular Carcinoma

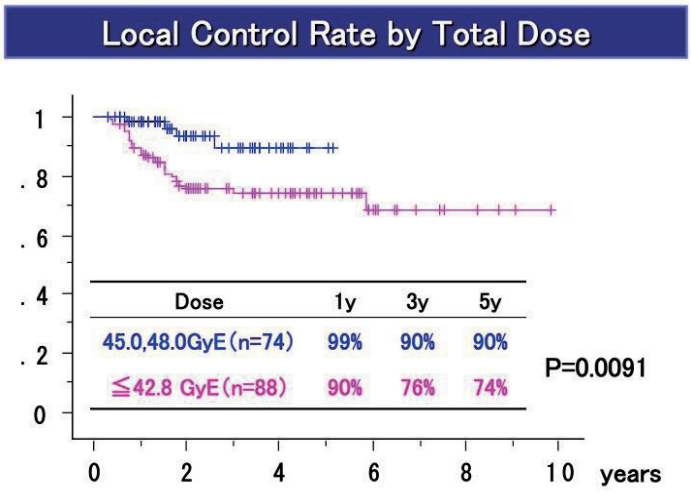
Shigeo Yasuda*, Yuka Isozaki, Shigeru Yamada, Tadashi Kamada

Research Center Hospital for Charged Particle Therapy

National Institute of Radiological Sciences, Chiba, Japan

*E-mail: yasudash@nirs.go.jp

Clinical trials of carbon ion radiotherapy (C-ion RT) for hepatocellular carcinoma (HCC) were conducted at the National Institute of Radiological Sciences (NIRS) in Japan between April 1995 and August 2005. In four clinical studies, we tried to determine the optimal dose and to shorten the treatment duration with 5 different fractionation schedules, using 15,12, 8, 4 and 2 fractionations. There have been no treatment-related deaths and no severe adverse events. As a result of these studies, the duration of treatment could be reduced from 5 weeks to 2 days. Two-fraction therapy is currently ongoing under the license of Highly Advanced Medical Technology. Between April 2003 and March 2014, 162 patients with HCC underwent 2 fraction C-ion RT. The patients were treated with a total dose range of 32.0-45.0 GyE. There were no cases of grade 4 toxicities. Local control rates were 94% and 91% at 1 year, and 84% and 73% at 3 years in the smaller tumor group (≦5 cm) and the larger tumor group (>5 cm), respectively(p=0.1126). The local control rates were 99% and 90% at 1 year, and 90% and 76% at 3 years in the higher dose group (≧45.0 GyE) and the lower dose group (≦42.8 GyE), respectively (p=0.0091). One and three-year overall survival rates were 99% and 74% in the higher dose group, and 90% and 59% in the lower dose group, respectively (p=0.0201). Because of the low toxicity and good local control rate, C-ion RT is a promising radical and minimally invasive therapeutic option for HCC.



Carbon Ion Radiotherapy of Pancreatic Cancer

Makoto Shinoto[1.2*], Shigeru Yamada[2]

[1] Ion Beam Therapy Center, SAGA-HIMAT Foundation, Tosu, Saga, Japan

[2] Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan

[*]E-mail: shinoto@saga-himat.jp

Pancreatic cancer is one of the most lethal cancers in the world. Complete surgical resection is the only curative treatment. However, only a small percentage of patients are candidate for surgical resection because of local progression or metastatic spread at the time of diagnosis. Even if a curative resection is performed, the disease usually recurs, and 5-year survival rates are less than 20%. Chemotherapy and/or chemoradiotherapy are usually selected as standard treatment for unresectable locally advanced pancreatic cancer. However, since pancreatic cancer is often resistant to chemotherapy and radiotherapy, the prognosis is dismal.

We initiated phase I/II clinical trial of pre-operative carbon-ion radiotherapy (C-ion RT) with 16 fractions in 4weeks for resectable pancreatic cancer in 2000 (Protocol 9906) (Figure1). The purpose of this treatment was to reduce the risk of postoperative local recurrence, which accounts for 40-80% of total recurrences. We established the tolerance and effectiveness of pre-operative C-ion RT and performed a clinical trial aimed at shortening the fraction size to 8 fractions in 2 weeks beginning in 2003 (Protocol 0203) (Figure 2). In this trial, 26 patients underwent pre-operative short-course C-ion RT and 21 patients were performed surgical resection. There was no local recurrence in irradiated field. On the other hand, 17 patients (65%) experienced distant metastases. The 5-year survival rates for all 26 patients and for 21 patients who underwent surgery were 42% and 52%, respectively. Currently, phase I clinical trial of pre-operative short-course C-ion RT combined with gemcitabine (GEM) is under way.

Figure1

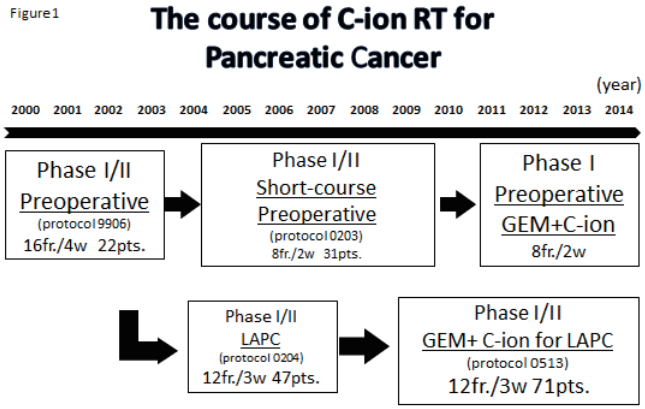
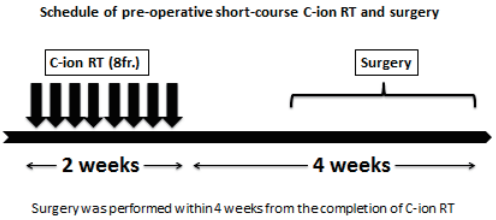


Figure2



In addition, we started phase I/II clinical trial for patients with locally advanced pancreatic cancer (LAPC). From 2004 we started dose escalation study of C-ion RT alone (protocol 0204). And next, from 2007 we started C-ion RT combined with GEM (protocol 0513) (Figure 3, 4). 72 patients with LAPC were treated with GEM and C-ion RT. Dose limiting toxicities were observed in 3 patients (4%): grade 3 cholangitis in one patient and grade 4 neutropenia in 2 patients. Only one patients experienced late grade 3 gastric ulcer and bleeding 10 months after C-ion RT. No other sever gastrointestinal toxicity was observed. Recommended dose of GEM was determined 1000mg/m2. Dose of C-ion RT combined with full dose of GEM (1000mg/m2) was safely escalated up to 55.2GyE. Two-year survival rates in all patients and in patients with high dose group (≥45.6GyE) were 35% and 42%.

Figure3

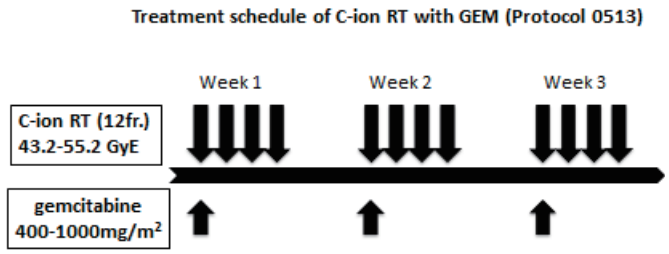
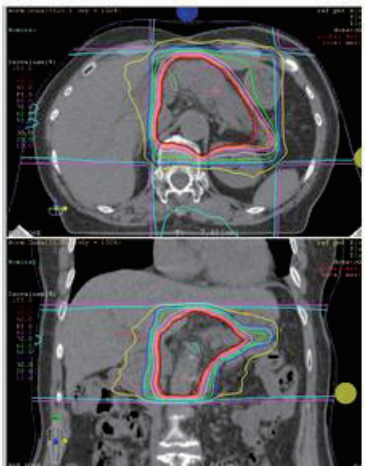


Figure4 Dose distribution of C-ion RT



In conclusion, our results indicate that C-ion RT was well tolerable and effective as pre-operative treatment for operable pancreatic cancer and definitive treatment combined with full dose GEM for LAPC. In the near future, more intensive local therapy with scanning method and full dose systemic therapy might be conduct improvement the outcome in patients with pancreatic cancer.

Carbon Ion Radiotherapy for Patients with Pelvic Recurrence of Rectal Cancer

Shigeru Yamada*, Makoto Anzai, Naomi Okada, Yuka Isozaki, Shigeo Yasuda, and Tadashi Kamada

Research Center for Charged Particle Therapy
National Institute of Radiological Sciences, Chiba, Japan
*E-mail: s_yamada@nirs.go.jp

Key words: Carbon-ion, Rectal Cancer, Recurrence

Purpose: To improve long-term local control and survival of locally recurrent rectal cancer, we have initiated a radiation dose-escalation trial using carbon ion beams. The purpose of this study is to evaluate the tolerance for and effectiveness of carbon ion radiotherapy in patients locally recurrent rectal cancer

Materials/Methods: Between April 2001 and August 2013, 214 lesions at 204 patients were enrolled onto this study. Criteria for trial eligibility were confirmation of locally recurrent rectal cancers without distant metastases based on CT, MRI and PET findings. Contraindications for trial entry included pelvic bone destruction. Carbon beams of 290, 350 and 400 MeV/nucleon energy were generated in the HIMAC synchrotron. The dose was determined as 67.2GyE and escalated to 70.4GyE, 73.6GyE. Of the 204 eligible patients, 149 were male and 65 female. Median age was 61.5 years. The predominant sites of relapse were 90 presacral , 77 side walll, 29 perineal and 18 soft tissue. Toxicities on organs were assessed according to the NCI-CTC classification. Tumor response was defined by the RESIST scoring system. Local recurrence was defined in terms of lesions occurring in the tumor bed. Survival curves were estimated by the Kaplan and Meier method.

Results: Ten patients received radiation dose at 67.2GyE, 18(+3) at 70.4GyE and 161(+6) at 73.6GyE. All toxicities in the 198 lesions at 189 patients were relatively few and mild in these patients. No grade 3 to 5 acute toxicity was observed. The local control rates in 197 lesions are 94% at three year and 88% at five years. Local control rates at 5 year were 96% at 73.6GyE. In terms of symptomatic response within 3 months after treatment, pain improved in 97% of the symptomatic cases. Pain relief was maintained at one year in 67%, 88% and 92% of the patients treated with 67.2GyE, 70.4GyE and 73.6GyE, respectively. The three and five year overall survival rate in 204patients were 71% and 44% respectively. Survival rates at 5 year were 20% at 67.2GyE, 24% at 70.4GyE and 51% at 73.6GyE. In the literature, the reported five-year survival rates for locally recurrent rectal cancer treated with resection were 20 to 40%.

Conclusions: Carbon ion radiotherapy seems to be a safe and effective modality in the management of locally recurrent rectal cancer, providing good local control and offering a survival advantage without acceptable morbidity.

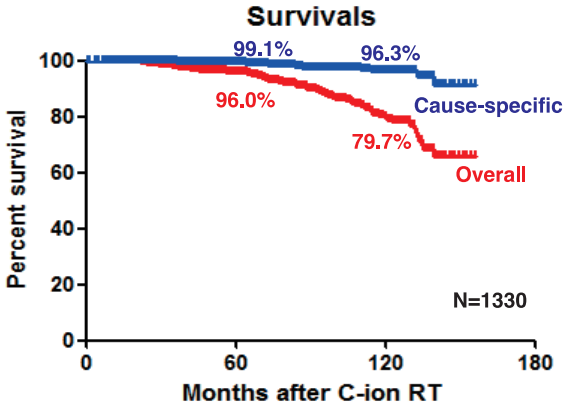
Carbon Ion Radiotherapy for Prostate Cancer

Hiroshi Tsuji*, Takuma Nomiya, Tadashi kamada, Hirohiko Tsujii
Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
*E-mail: h_tsuji@nirs.go.jp

Prostate cancer is one of suitable indications of the carbon ion therapy (C-ion RT) because it can offer better dose distribution and superior anti-cancer effect than other radiation therapies. In fact, we could obtain quite favorable outcomes through initial clinical trials and the following practical treatment. The first clinical trial for prostate cancer was started in 1995 and two phase I/II dose escalation studies with a fractionation of 20 fractions over five weeks were conducted to establish techniques using carbon ion beams to determine the optimal dose in this fractionation. Then, a phase II study of 20 fractions was performed to validate the feasibility and efficacy of C-ion RT delivered in 20 fractions, which was successfully completed in 2003. Thereafter, a study of hypofractionated C-ion RT in 16 fractions over 4 weeks was performed. Consequently, the incidence of late radiation toxicity decreased without an increase in tumor recurrence. Currently, hypofractionated radiotherapy in 12 fractions over three weeks with scanning irradiation is being evaluated in clinical practice.

Up to February 2014, 2011 patients underwent C-ion RT, including 562 patients treated with 20 fractions, 1107 patients treated with16 fractions and 342 patients treated with 12 fractions. Of those, 1,330 patients who received the C-ion RT after the start of the phase II study according to the recommended strategy in regard to administration of hormone therapy were analyzed. About a half of those were categorized as high-risk. The five-year overall survival rate and biochemical relapse- free rate in the entire group were 96.0% and 91.2%, respectively. All risk factors, such as pretreatment PSA, clinical T-stage, and Gleason's score had a significant influence on both biochemical control and patient survival. Biochemical control was not affected by the alteration of dose fractionation. Incidences of radiation toxicity due to C-ion RT were quite low. No patient developed grade 3 or higher toxicity in 16-fraction treatment and grade2 rectal toxicity was developed in less than 1% of the patients.

Recently irradiation using the scanning carbon-ion beam became available at the NIRS. It can provide even better dose distribution than the conventional passive irradiation and the treatment efficiency has also improved because no specific absorber or collimator for each patient is necessary for the scanning irradiation. Currently, all the prostate cancer patients undergo the scanning carbon ion therapy of 12 fractions over 3 weeks at the NIRS.



The number of facility available for the C-ion RT for the prostate cancer has gradually increased in Japan. A new study group was organized by the 4 running C-ion RT facilities of NIRS in Chiba, HIBMA in Hyogo, GHMC in Gunma, and HIMAT in Saga. It is expected to conduct prospective multi-nstitutional clinical trials in various tumor entities including prostate cancer to prove the usefulness of C-ion RT.

Carbon Ion Radiotherapy for Locally Advanced Uterine Cervical Cancer

Masaru Wakatsuki[1*], Shingo Kato[2], Shintaro Shiba[1]

[1]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan

[2]Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, Japan

[*]E-mail: waka@nirs.go.jp

Cisplatin-based concurrent chemoradiation therapy (CCRT) has become the standard treatment for locally advanced cervical cancer. However, intracavitary brachytherapy might not deliver a sufficient dose to extensive or bulky tumors and this might cause local failure for patients with locally advanced disease. As for clinical trials of C-ion RT for locally advanced cervical cancer, 5 have already been completed.

Between June 1995 and January 2012, 62 patients in 3 clinical trials were treated with C-ion RT for locally advanced squamous cell carcinoma of the uterine cervix. The numbers of patients with stage IIB, IIIB, and IVA disease were 14, 38, and 10, respectively. Median tumor size was 6.4 cm (range, 4.0–12.0 cm). Median overall treatment time was 36 days (range, 32 to 48 days). The 5-year overall survival rate and local control rate were 55.7% and 76.7%, respectively (Figure 1). Even though the tumors of our cases were bulky (median size, 6.4 cm) and 2 of the 3 trials were dose-escalation trials, the local control rate was favorable; nonetheless, distant metastases frequently occurred, and the 5-year overall survival rate was still considered unsatisfactory.

C-ion RT for uterine adenocarcinoma has been targeted primarily at non-resectable tumors, and a total of 61 patients with locally advanced adenocarcinoma of the uterine cervix were enrolled in a dose-escalation trial between April 1998 and February 2010. Six of the 61 patients were subsequently disqualified and excluded from the analysis. The number of patients with stage IIB, IIIB, and IVA disease were 20, 33, and 2, respectively. Pelvic lymph node metastases were found in 25 of the patients. Median tumor size was 5.5 cm (range, 3.0-11.8 cm). The 5-year local control rate, local control rate including salvage surgery, and overall survival rate were 54.5%, 68.2%, and 38.1%, respectively (Figure 2). Although the number of patients in this study was small, the results support the need for further investigations to confirm the therapeutic efficacy.

Hence, we are now conducting new clinical trials of C-ion RT with concurrent chemotherapy for locally advanced cervical cancer.

Figure 1

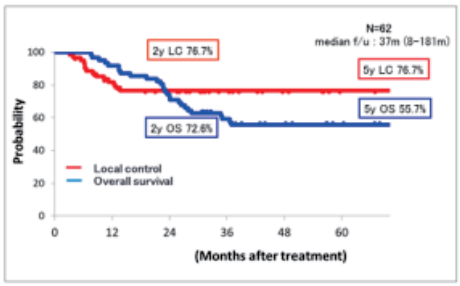
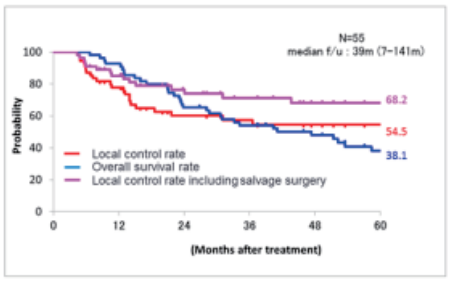


Figure 2



Review of Biology Related to Heavy-Ion Radiotherapy

Eleanor A. Blakely

Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA
E-mail: eablakely@lbl.gov

An international effort has provided four decades of laboratory-based radiobiology in support of clinical radiotherapy with heavy-ion beams. Implementation of any new radiation modality to treat human cancer safely and effectively requires rigorous quantitative investigation of dose-dependent acute and late tissue effects, as well as studies of underlying molecular and cellular mechanisms functioning under specific radiation treatment delivery protocols. This presentation will briefly review the historical origins and the evolving developments of the scientific effort to acquire this database. Discoveries of key novel observations and identification of unique biological responses triggered by molecular damage clustered along particle tracks, and benefits from significant technical improvements in targeted imaging of tumor biology, have both led to a continual optimization of heavy-ion radiotherapy for specific individual tumor sites. A systematic experimental evaluation of precise dose delivery methods, and of dose fractionation protocols further enhanced clinical outcome. The major radiobiological contributions to implementing the world's first carbon ion therapy clinical trial spearheaded by the National Institute of Radiological Sciences in Japan during the past 20 years will be highlighted.

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Recent Progress of Particle Radiation Biology

Walter Tinganelli[1,2] Marco Durante[1*] Ryoichi Hirayama[2], Michael Krämer[1], Andreas Maier1, Wilma Kraft-Weyrather[1], Yoshiya Furusawa[2], Emanuele Scifoni[1]

[1] GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Darmstadt 64291, Germany

[2] National Institute of Radiological Sciences, Chiba, Japan

[*]E-mail: M.Durante@gsi.de

Solid tumors present regions with severe oxygen deprivation. These hypoxic regions are resistant to both chemotherapy and radiotherapy. Increased radiosensitivity as a function of the oxygen concentration is well known for X-rays. It has also been demonstrated that radioresistance in anoxia is reduced using heavy nuclei rather than conventional X-rays. However, the dependence of the oxygen enhancement ratio from radiation quality in the regions of intermediate oxygen concentrations, those normally found in tumors, had never been measured and biophysical models were based on extrapolations from X-ray data. Here we present a complete dataset of mammalian cell survival exposed to different ions in oxygen concentration ranging from normoxia to anoxia. Experiments were performed at HIMAC, GSI, and HIT (Fig. 1). The data were used to generate a model of the dependence of the oxygen enhancement ratio on oxygen concentration and particle energy and then implemented in the ion beam treatment planning system to prescribe uniform cell killing across volumes with heterogeneous radiosensitivity. The adaptive treatment plans have been validated at HIMAC and GSI, both in forward and inverse planning, using a biological phantom where cells can be irradiated simultaneously at three different oxygenation conditions. This treatment plan will be used for painting by voxel of hypoxic tumors visualized by functional imaging. This work was generously supported by the International Open Laboratory at NIRS.

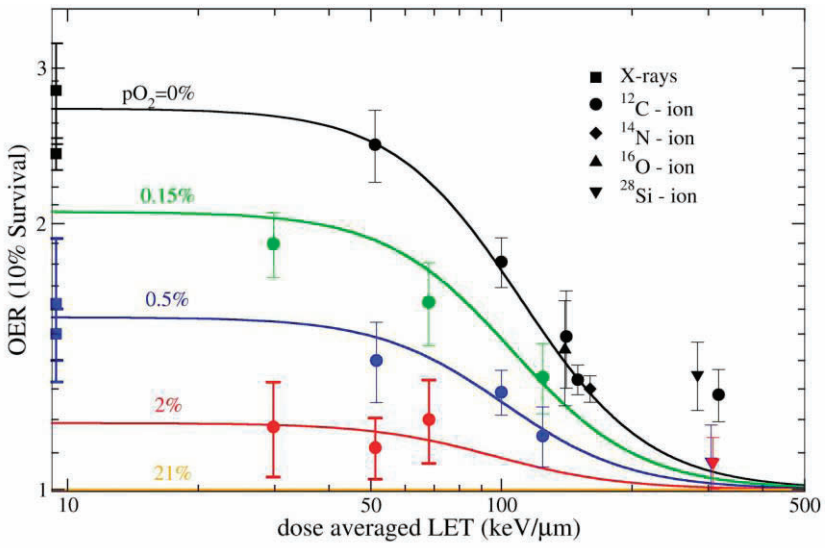


Figure 1. Measured oxygen enhancement ratio (at 10% survival level) in Chinese Hamster Ovary cells exposed to different heavy ions at HIMAC, GSI, and HIT. Picture courtesy of Dr. Furusawa, Dr. Hirayama, Dr. Tinganelli and Dr. Scifoni.

DNA Repair and Checkpoint Pathways in Human Cells Exposed to Heavy Ion Radiation

Hirohiko Yajima[1*], Lian Xue[2], Cuihua Liu[1], Hiroshi Fujisawa[1,3], Nakako Izumi Nakajima[1]

[1]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
[2]School of Public Health, Medical College of Soochow University, Suzhou, China
[3]School of Engineering, The University of Tokyo, Tokyo, Japan
[*]E-mail: hyajima@nirs.go.jp

DNA double strand breaks (DSBs) induced by ionizing radiation (IR) are deleterious damages, and it is known that high linear energy transfer (LET) radiations, such as heavy ion beams, induce complex DSBs. Two major pathways repair DSBs in human cells, non-homologous end-joining (NHEJ) and homologous recombination (HR), and the efficiency of NHEJ in repairing complex DSBs was shown to be diminished. An early step in HR is the generation of 3'-single strand DNA (ssDNA) via a process called DNA end resection. We show that the complexity of DSB ends drastically alters the balance between the two repair pathways, and enhances end resection. More than 80 % of complex DSBs are subjected to resection in heavy ion particle tracks, and around 20-40 % of G1 cells exhibit resection signals. Furthermore, we investigated how the enhanced resection influences the function of ATR pathway, since it has been well accepted that the ssDNA exposed by resection can be a signal for the activation of ATR kinase. Although it has been elucidated that ATM is a primary kinase in the G2/M arrest regulation in response to IR, our results of G2/M checkpoint assays show that ATR pathway plays a pivotal role and functions in a dose- and LET-dependent manner to regulate the early G2/M checkpoint in ATM-deficient cells. Collectively, our study reveals that the complexity of DSB end structure is a critical factor that drastically changes repair pathway preference, and provokes the ATR-dependent signaling.

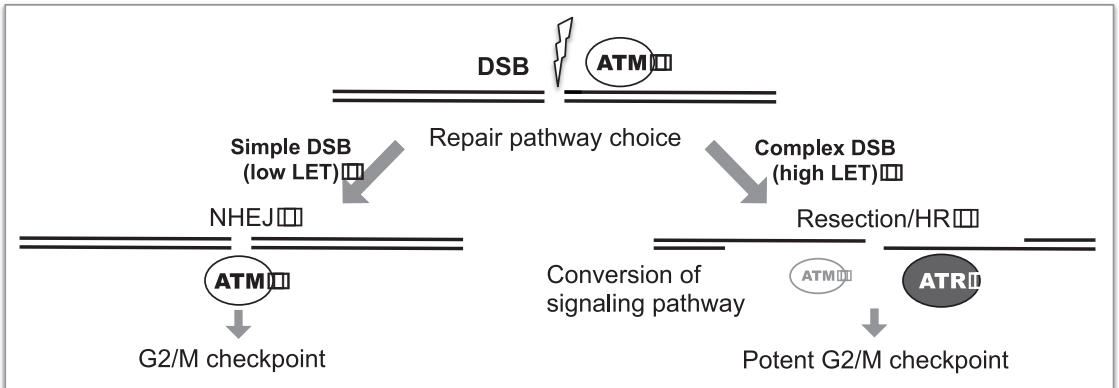


Figure. DSB repair pathway choice and G2/M checkpoint signaling

The Combination of Carbon-Ion Radiotherapy and Immunotherapy in *In Vivo* Mouse Models

Takashi Imai* and Takashi Shimokawa

Advanced Radiation Biology Research Program, Research Center for Charged Particle Therapy
National Institute of Radiological Sciences, Chiba, Japan
*E-mail: imait @nirs.go.jp

Clinical trials of carbon-ion radiotherapy have reported many favorable outcomes against several types of malignant tumors. However, distant metastases that are detected after local treatment remain a major challenge that needs to be overcome to improve long-term survival. It has been reported that systemic micrometastases may already be present at the time of treatment. If this theory is correct, then the concurrent use of systemic medications in combination with carbon-ion radiotherapy could improve survival by inhibiting these micrometastases. In this symposium, I would like to describe investigations that we have performed on the effects of dendritic cells immunotherapy provided in combination with carbon-ion radiotherapy.

First, we analyzed the gene expression profiles of murine implanted tumors to identify molecular pathways that are induced by carbon-ion irradiation and by γ-ray irradiation as a control. The comprehensive gene expression profiles of metastasized cells after local radiotherapy were more similar to each other than to their corresponding primary tumors. We also detected that carbon-ion irradiation up-regulates more membrane-associated immunogenic molecules than does γ-ray irradiation. These results led us to hypothesize that local carbon-ion irradiation induces a systemic response. Therefore, the combination of carbon-ion radiotherapy with systemic immunotherapy could have a high curative effect, even for distant metastases. We, then, used multiple *in vivo* murine metastatic models to analyze the efficacy of the combination of dendritic cells injection and carbon-ion irradiation. Carbon-ion irradiation alone and dendritic cells injection alone partially suppressed lung metastases under conditions in which these did not have any significant effect on the growth of the primary implanted tumor. On the other hand, the combination of these treatments significantly reduced the number of lung metastases under similar conditions. It is interesting that the lung tissues of the non-treatment group showed increased expression of particular proinflammatory molecules over time, while the lung tissues of the combination therapy group showed poor expression of these molecules. Because our results clearly indicate that the combined therapy was an effective means of repressing metastasis, this approach could have important clinical implications.

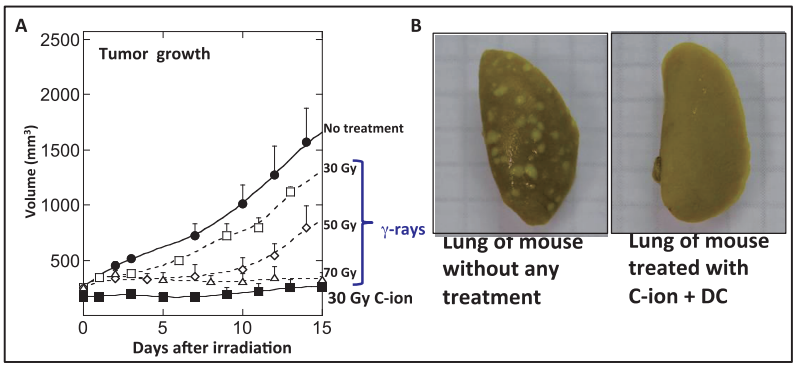


Figure Effects of the combination therapy in the NRS1/CSH model.
A. Tumor growth curves after various single doses of carbon ions or gamma rays.
B. Macroscopic images of lung metastases 2 weeks after start of treatment.

Day 2

Clinical Activities at the Italian National Center for Oncologic Hadrontherapy CNAO

Roberto Orecchia[1, 2*], Cristina Bono[1], Maria Bonora[1], Elisa Ciurlia[1], Maria Rosaria Fiore[1], Angelica Facoetti[1], Piero Fossati[1, 2], Alberto Iannalfi[1], Barbara Vischioni[1], Viviana Vitolo[1], Francesca Valvo[1]

[1]National Center for Oncologic Hadrontherapy, Pavia, Italy
[2]European Institute of Oncology, Milan, Italy
[*]E-mail: roberto.orecchia@cnao.it

After the conclusion of the experimental phase at the end of 2013, after being allowed the clinical use of proton and carbon ions beams by Italian Health Authorities, at the CNAO (National Center for Oncological Hadrontherapy) about 420 patients have been treated in the frame of 30 clinical trials. The percentage of treatments with carbon ions has been increasing mostly in the last months to reach about the 75% of the whole activity. All the body districts have being treated up to now, according to several clinical procedures concerning different pathologies. An important experience has been gained in the treatment of bones and soft tissues chordomas and chondrosarcomas, both of the pelvis and of the skull base, renowned for their high intrinsic radio resistance. These diseases have been among the first treated by the CNAO and have been reaching almost the 50% of the faced cases. In the clinical records, patients with histologic diagnoses of chordoma underwent to hadrontherapy after one or more surgical R2 resections with macroscopic disease or with recurrences. These patients have been treated by proton beam, using conventional fractionaction up to 70-74 GyE, or carbon ion, by hypofractionated schedule in 16 fractions. The other relevant category of treatments is salivary glands tumours, treated with carbon ion only, using the same protocol already extensively applied in Chiba. Re-irradiation has been applied, with mostly lesions seated in the head and neck region with different histology. The great majority of the re-treatments are provided with carbon ion therapy. Given the complexity of such treatments, and their radical intent, the prescription dose has to be calculated on each single case on the basis of the previous radiotherapy, even if a range of doses and of sessions' number is established by protocols limits.

Each patient is followed along the therapy cycle, at the end and every three months to register the acute and late toxicity according to the CTCAE scale. The imaging control is also foreseen to evaluate the radiological response following the RECIST criteria. Most of patients affected by head and neck tumours undergo to a PET with methionine to define at the best the target volumes. The hadrontherapy treatment demonstrated to have a good tolerance for the most of patients of CNAO with a very low rate of G3 toxicity. The average follow up is of 15 months. Preliminary results on toxicity and tumor control will be presented.

The running clinical trials, besides chordoma and chondrosarcoma, salivary glands tumours, and recurrent cervico-cephalic area tumors, focus on primary and recurrent brain tumours (including atypical and malignant meningiomas), high risk prostate carcinoma (T3 stage, PSA >20ng/ml, Gleason score of 8 to 10) with CIRT and with a CIRT boost followed by IG-IMRT, recurrences of rectal cancers, primary and secondary orbital tumors (including eye melanoma) and primary pancreatic cancers. The first case of this last cited disease has recently been treated through an organ motion control system which made possible to follow and control the breathe of patient coupling it with the irradiation time through active scanning. Next challenging step for the CNAO will be the beginning of proton beam therapy in pediatric tumors.

Clinical Experience of SAGA HIMAT

Sho Kudo[1]*, Yoshiyuki Shioyama[1], Hiroaki Suefuji[1], Akira Matsunobu[1], Makoto Shinoto[1], Shingo Toyama[1], Masahiro Endo[1], Mitsutaka Kanazawa[1], Hiroshi Sato[1], Tadahide Totoki[1]

[1]Ion Beam Therapy Center, SAGA HIMAT Foundation, Tosu, Saga, Japan
*E-mail: kudo-sho@saga-himat.jp

SAGA HIMAT stands for Saga Heavy Ion Accelerator in Tosu. It is located in Tosu City, Saga Prefecture, Japan. The SAGA HIMAT Project is a collaborative work among the local (Saga prefectural, Fukuoka prefectural and Tosu city) governments, regional industries, and universities in Kyushu area. The initial cost was about 15 billion yen which was covered by donations, investments, and some by governmental aids.

At SAGA HIMAT, carbon ions are accelerated by two linear accelerators and a synchrotron, and they are transported to the treatment rooms A and B. The range of extracted energy is 140–400MeV/u. The room A has horizontal and 45 degree oblique and the room B has horizontal and vertical beam lines, where broad beams are used and each outlet measures 15x15cm. As preparations, we make an immobilization device adjusted to the patient's body and a beam compensation bolus adjusted to the shape of the irradiation field.

SAGA HIMAT is a standalone outpatient clinic specialized for carbon ion cancer therapy. The patients initially visit a cancer treatment facility of their choice and will be referred to our place. All are treated as out-patients. If necessary, some patients are admitted to nearby affiliated hospitals and commute to SAGA HIMAT for the therapy. After completion of the therapy, the patients will be observed regularly both at our clinic and at the initial institute.

The radiology departments of three nearby university hospitals, Saga, Kurume, and Kyushu are particularly committed to the project. They train and provide the medical staff to SAGA HIMAT. They also have ion beam therapy consultation clinics and select the patients for carbon ion therapy. In order to perform the patient referral and treatment smoothly, we exchanged medical agreements with many other institutes, including university hospitals and major cancer institutions.

Our treatment protocols are mainly based on the results from the National Institute of Radiological Science (NIRS) in Chiba Japan. Furthermore, review boards for 9 different organs (1.urological, 2.head and neck, 3.lung, 4.liver, 5.pancreas, 6.bone and soft tissue, 7.recurrent rectal, 8.esophageal, 9.gynecological tumors) were made to check and discuss the treatment protocols and the clinical results. The board members consist of cancer authorities from outside facilities.

We started treatment of prostatic cancers in August 2013, head and neck cancers and bone and soft tissue tumors in December 2013, and respiratory gated treatment for lung, liver, and pancreas cancers in March 2014. We have treated 502 patients by the end of November 2014, including 345 prostatic, 42 lung, 41 liver, 32 head and neck, 22 pancreatic, 12 bone and soft tissue, 2 renal and 4

local recurrent rectal cancers.

We are now preparing for the treatment of esophageal and gynecological cancers. We have also started preparations for another treatment room (room C) which will be ready for scanning beam therapy in 2017. Then, we plan to treat over 800 patients a year in near future. We hope carbon ion beam therapy will become one of the major choices to treat cancer patients and SAGA HIMAT will become a model case of multi-facility collaboration for cancer treatment.

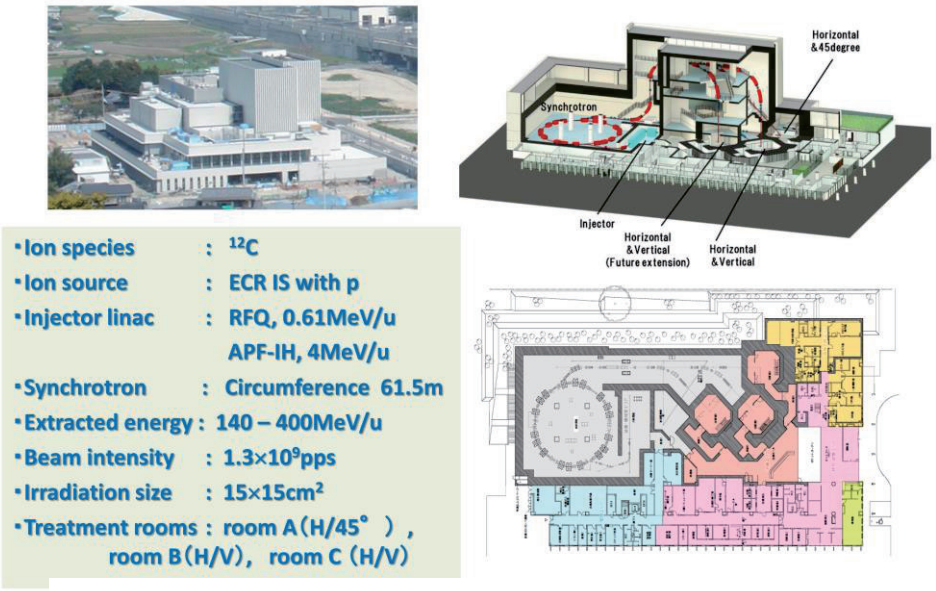
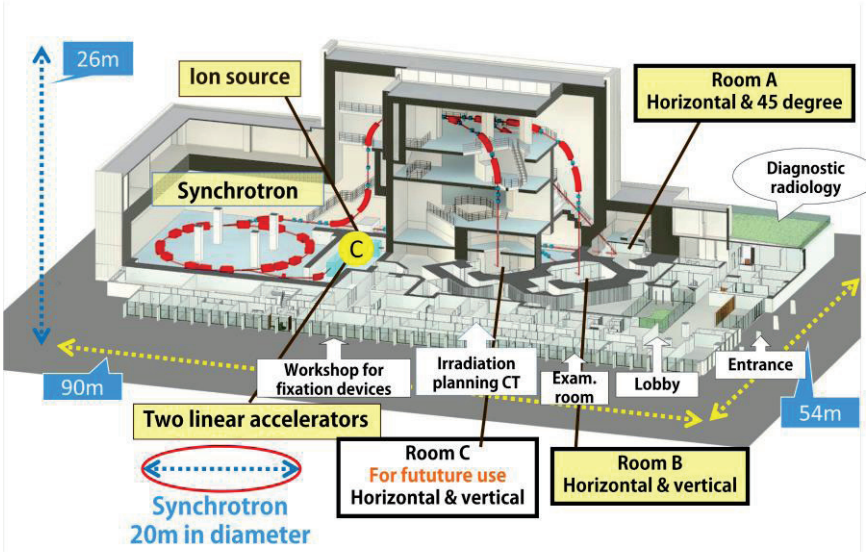


Fig.1 SAGA HIMAT layout and specifications



Alternative Fig.1 SAGA HIMAT layout

Proton and Carbon Irradiation in Shanghai Proton and Heavy Ion Center

Guo-Liang Jiang*, FACR (Hon.), Jiade J. Lu, Shen Fu, Michael F. Moyers

Shanghai Proton and Heavy Ion Center, China
*E-mail: guoliang.jiang@sphic.org.cn

Shanghai proton and heavy ion center (SPHIC) started to treat patients in June, 2014 after 10-year endeavor.

SPHIC is now facilitated with Siemens particle therapy system, which includes a synchrotron generating proton of 48-221 MeV and carbon of 85-430 MeV beams, 4 treatment rooms with 90-degree and 45-degree beams, robotic arm for patient set-up, on line imagers, raster beam scanning, and Syngo PT planning system. Besides, the modern diagnostic radiology facilities, including CT, MRI, SPECT and PET/CT, are also available there.

SPHIC has recruited high level staffs from the United States and Singapore, and also from China to form a strong team of radiation physics and clinical radiation oncology. Those well-trained and experienced staffs ensure the success of SPHIC in treating patients with particles.

Required by Chinese Food and Drug Administration (CFDA), from June, 2014 SPHIC has been carrying out a registration clinical trial to verify the toxicity and efficacy of proton and carbon irradiation for cancers published in the literature. The number of patients needed for this trial was 35. We have already enrolled 35 patients and completed irradiation at the end of Sept., 2014. Among 35 patients 31 are males and 4, females with a medium age of 69 years (36-80). The lesions were not fit to surgery in 17 patients (49%) due to residuals after surgery, or technically unresectable (14), and anesthesia contraindication because of the comorbidity (cardiovascular diseases) (3). There were 10 patients with head and neck cancers (chordoma or condrosarcoma at the base of skull, or adeno-cystic carcinoma in nasal cavity); 4 patients with primary or metastatic lung cancers; and 21 patients with prostate carcinoma, hepatocellular carcinoma or retroperitoneal liposarcoma. We have used proton in 13 cases and carbon beam in 22 cases. Overall, the patients tolerated irradiation very well and none of 35 patients experienced grade 3 or higher of CTC adverse effects, which were related or possibly related to particle therapy. All patients completed the planned doses with no interruptions due to the acute toxicity.

For moving targets in the liver and lung abdominal compression, active breath coordinator (ABC) and respiratory gating by Anzai have been tested successfully.

The patients will be followed up for 3 months longer after irradiation to observe the toxicity and efficacy. After getting CFDA approval by the spring of 2015 SPHIC could treat patients with proton and carbon ion routinely.

Which of the Two Particle Therapies (Carbon Ions and Protons) is Better in Cancer Treatment?

Nobukazu Fuwa*, Yusuke Demizu, Osamu Fujii, Kazuki Terashima, Masayuki Mima, Masaru Takagi, Dongcun Jin, Fumiko Nagano and Takahiro Waki

Hyogo Ion Beam Medical Center, Tatsuno, Hyogo, Japan

*E-mail: n.fuwa@hibmc.shingu.hyogo.jp

Abstract

The Hyogo Ion Beam Medical Center (HIBMC) is the first institution in the world that can use both protons and carbon ions. The differences between carbon ions and proton beams were as follows;

1. Biology

Carbon ions has some advantages on radiation biology compared to proton beams; higher relative biological effectiveness (RBE), lower oxygen enhancement ratio (OER), higher linear energy transfer (LET), lower cell cycle dependence, and lower recovery of lethal (sublethal) damage repair. However, the therapeutic gain factor (TGF) which is considered to be one of the most important factors in clinical use may be changed from tissue (tumor) to tissue (tumor). Therefore, the superiority of carbon therapy which has some biological advantages does not always reflect the clinical treatment results.

2. Physics

Carbon ions beam has a better penumbra compared to proton beams. Carbon ions always shows better dose distribution under the same conditions. On the other hand, carbon ions facility costs much more in both construction and running compared to proton beams facility, and cannot use gantry system which can be used in proton therapy. The cost of proton beams facility which has two treatment rooms is about 8 billion Yen, on the other hand, that of carbon ions facility is about16 billion Yen. From the viewpoint of economical situation, carbon ions facility has some problems.

3. Clinical use

As of the end of 2012, we have treated 5381 patients in total. Retrospective clinical outcomes and late toxicities of stage I lung cancer, malignant melanoma and adenoid cystic cancer of the head and neck, liver cancer, and soft tissue sarcomas have not shown no significant differences between carbon ions and proton beams. Therefore, the indications of both therapies have not been unclear at present.

Large sized soft tissue malignant tumors including many hypoxic cells which are considered to be resistant to proton beams might be suitable for carbon ions therapy. Conversely, pediatric cancer might not be suitable for carbon ions therapy which has some biological advantages compared to proton.

Considering the better dose distribution of carbon ions, the patients with poor pulmonary and liver function might be suitable for carbon ions therapy compared with proton beams therapy.

4. Conclusions

Carbon ions therapy has some advantages on radiation biology and physics compared to proton beams. However, its cost is higher and the indication of carbon ions has not been unclear.

It is hard to say which of the two particle therapies (carbon ions and protons) is better in cancer treatment. Randomized controlled clinical trials to compare carbon ions and protons are warranted.

Current Status of MedAustron

Ramona Mayer[1], Stanislav Vatnitsky[1]

[1]EBG MedAustron, Wiener Neustadt, Austria

*E-mail: ramona.mayer@medaustron.at

MedAustron is a synchrotron based dual particle beam facility in Wiener Neustadt, Austria. The synchrotron that was developed in collaboration with the European Organization for Nuclear Research (CERN) is providing protons with energies from 60 MeV to 250 MeV and carbon ions from 120 MeV/u to 400 MeV/u with the continuous scanning beam delivery systems. Two treatment rooms are equipped with fixed beams (horizontal fixed beam; horizontal and vertical fixed beam). The third room houses the proton gantry with an angular workspace from -10° to 180°. The fourth room is equipped for non-clinical research with protons and carbon ions and supports proton experiments with higher energies, up to 800 MeV. Apart from special experimental equipment the non-clinical research room provides identical medical technology for reliable translation of research results into clinical routine.

Currently the proton beam is transported to the first treatment room and the beam delivery system is in a tuning process to comply with clinical requirements to be prepared for medical commissioning. Patient alignment system (PAS) comprising of ceiling-mounted robotic positioner, imaging ring device and collision avoidance system is under acceptance testing in two fixed beam rooms. The use of the MedAustron PAS allows 2D/3D and later CBCT patient position verification for non-isocentric treatments with minimum air gap providing better lateral penumbra especially at low proton energies.

A package of integrated medical software components – Oraion is integrated at MedAustron with the treatment planning System (TPS) from RaysSearch Laboratories. TPS RayStation® will be used at MedAustron for collision-free planning of all treatments including protons and carbon ions as well as conventional treatments as back-up solution. The clinical version of the proton module will be installed and accepted in February 2015. The carbon ion planning module builds on the current pencil beam scanning functionality for protons. The module optimizes the scanning pattern for discrete as well as line scanned beams. For physical dose calculation two algorithms are used, pencil beam and Monte Carlo, to serve both normal clinical use as well as research needs. The system will also be capable of optimizing biologically effective dose. The commissioning of RayStation® carbon module is scheduled for 2016.

The first patient treatment is scheduled 2015/2016. Once the centre is in full operation, it will be possible to treat up to 1,200 patients per year.

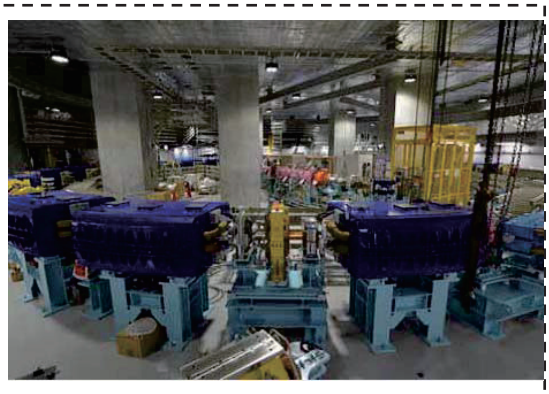
Current Status of i-ROCK (Kanagawa)

Yuko Nakayama*, Tetsuo Nonaka, Nobutaka Mizoguchi, Toyokazu Hayakawa, Shinichi Minohara, Yohsuke Kusano, Eri Takeshita, Haruhiko Nakayama, Makoto Akaike

Promotion Division of Heavy Ion Facilities, Kanagawa Cancer Center, Yokohama, Japan
*E-mail : nakayamy@kcch.jp

Our new state-of-the-art carbon-ion radiotherapy facilities, named i-ROCK, will start its clinical operation in December 2015. The construction of i-ROCK was completed, and the imports and the installation of the devices were finished as scheduled. The beam tuning of the injector has just been started. i-ROCK, the only parallel establishment with a Cancer Center in Japan, is the fifth carbon-ion radiotherapy facilities in Japan. Kanagawa Cancer Center (KCC) is located in Yokohama, a capital of Kanagawa prefecture, has developed into Japan's 2nd largest city with a population of about 4 million. The location of KCC benefits from an excellent and efficient public transportation network covering the entire area of Kanagawa Prefecture and extending into Tokyo Metropolitan District, including Tokyo Station and Tokyo International Airport. Therefore, KCC is deemed to stand at an ideal location for receiving outpatients from local, regional, and even distant areas. One of the major missions of the forthcoming radiotherapy facilities is to provide the latest medical treatment in an outpatient setting, and it is expected that 880 patients a year will be treated at its full capacity. i-ROCK will be managed and operated in close cooperation and coordination with other departments in KCC, with the help of its cancer specialists, who will design high-level medical treatment for various types of cancer. The combination of i-ROCK and the high-precision radiation therapy units of the KCC will provide the full range of radiation oncology center services, from which appropriate treatment strategies will be selected for each patient. i-ROCK has 4 treatment rooms. In each room, patients are automatically setting to the treatment position by robotic couch having 7 axes. Self-propelled CT is also installed in each room for high-precision carbon-ion radiotherapy. We will start carbon-ion radiotherapy using spot scanning method. i-ROCK will be the first specialized facilities for scanning method in Japan.

The building of i-ROCK



The accelerator

Current Status of KHIMA Project

Chul-Koo Cho[1*], Sang-Hoon Nam[2], Won-Gyun Jung[2], Geun-Bum Kim[2], Mi-Sook Kim[1]

[1]Korea Cancer Center Hospital, KIRAMS, Korea
[2]Korea Heavy-ion Medical Accelerator Project, KIRAMS, Korea

[*]E-mail:chcho@kirams.re.kr

On behalf of Korea Heavy-ion Medical Accelerator (KHIMA) Project, current status will be reviewed and discussed about design, development, construction, and clinical study for heavy-ion treatment.

Synchrotron design and development will be presented in the physical aspect of whole accelerator system including ion source, injector, main ring and beam transport. After changing main accelerator from superconducting cyclotron to synchrotron, a lot of efforts have been made with help from domestic and foreign existing center and dedicated laboratory to heavy-ion therapy.

The process of the establishment of the project will be introduced from administrative matter, to building construction, to project organization. Admitting there is some consideration unique to the policy and the regulation under Korea government, most of the process set-up would be based on those from existing heavy-ion therapy center abroad.

Many in-house developments will be reviewed from the clinical point of view including 6D robotic positioning, low dose target localization and monitoring, and real time beam verification.

Clinical study on heavy-ion treatment has been rigorously performed for appropriate system design and successful operation of Korea heavy-ion therapy center. Starting from patient estimation, related clinical requirements for system design, biological experiment for intercomparison database, and clinical protocol have been set up. Especially, comparative study is going on between conventional SBRT including cyberknife and carbon beam therapy by focusing on enhancement of clinical effectiveness.

Many feedbacks would be appreciated very much for this presentation regarding various areas from accelerator to radiobiology, as your experience and effort are valuable to guide our first heavy-ion therapy in Korea and they are really counted for our project.

Particle Radiotherapy from NCI Point of View

Bhadrsain Vikram

National Cancer Institute, National Institutes of Health, USA

E-mail: Vikramb@mail.nih.gov

The NCI sponsors research in all aspects of cancer prevention and control, ranging from fundamental research to multinational clinical trials. In the context of Radiation Oncology some priority areas include: #1) research aimed at increasing the tumor control in patients with locally advanced cancers such as glioblastoma, lung cancer and pancreatic cancer, #2) research aimed at increasing the tumor control in patients with metastatic cancers and #3) research aimed at decreasing the adverse effects of treatment in patients with curable cancers such as low-risk prostate cancer and HPV positive head and neck cancer.

For #1 one approach includes discovering and testing drugs that can safely enhance the efficacy of radiation therapy; another includes particle therapy such as with protons and carbon ions.

For #2 one approach includes using radiation to modulate the immune response to cancer; another involves adding radioactive payloads to drugs that target cancerous tissues according to pharmacodynamic studies; a third approach includes techniques such as photodynamic therapy and hyperthermia.

For #3 one approach includes discovering and testing drugs that can mitigate the adverse effects without decreasing the effectiveness of radiotherapy and chemotherapy; another involves physical techniques such as proton therapy and intensity modulated photon therapy.

During the last quarter of the twentieth century the NCI extensively supported research in proton and other charged particle radiation therapy at Harvard University, University of California Berkeley, Los Alamos National Laboratory, etc. Surprisingly, even though the first dedicated proton and carbon ion therapy facilities became operational 20-25 years ago they have generated no “level one” evidence from prospective randomized trials. In contrast, several randomized trials conducted almost 20 years ago firmly established that adding drugs such as cisplatin and temozolomide to photon radiation therapy prolonged the survival of patients with several kinds of cancer such as cervix, head and neck and brain cancers.

Within the last few years, therefore, the NCI has sponsored several prospective randomized trials to test whether the survival of patients with non-small cell lung cancer and glioblastoma is better or worse after proton radiotherapy than photon radiotherapy. In addition, several randomized trials are now studying whether the quality of life of patients with prostate cancer, head and neck cancer, etc is better after proton radiotherapy than photon radiotherapy.

Recently the NCI Board of Scientific Advisors approved up to 2 million dollars for sponsoring a prospective randomized trial to determine if the survival of patients with locally advanced pancreatic cancer was better or worse after carbon ion radiotherapy than photon radiotherapy. This was prompted by the promising results reported by NIRS investigators at several international meetings. The NCI has recently also decided to award two planning grants to US institutions that are interested in establishing a light ion radiotherapy facility for conducting physics, biology and clinical research with not only protons and carbon ions but also others such as helium and oxygen.

Planning for a Heavy Ion Radiotherapy Research and Treatment Center in Colorado

Jac A. Nickoloff[1*], Susan M. LaRue[1], Brian Kavanagh[2]

[1]Environmental & Radiological Health Sciences, Colorado State University, Fort Collins, CO, USA
[2]Department of Radiation Oncology, University of Colorado School of Medicine, Denver, CO, USA

[*]Email: J.Nickoloff@colostate.edu

Physical and biological features of carbon ion radiation suggest greater treatment efficacy for many tumor types, especially those within or near sensitive structures (brain, head and neck, heart, spinal cord, lower GI tract), and this has been confirmed by a combined 30+ years of clinical experience in Japan and Germany. Nonetheless, carbon ion radiotherapy (CIRT) is still a relatively new clinical modality and many research questions remain at the fundamental levels of cells and molecules, tumor response in small animal models, and in clinical trials. CIRT facilities are expensive and this is certainly a key factor that has delayed introduction of CIRT in the US. However, in the past several years, the success of CIRT in Japan and Germany has spurred the US radiation oncology community to reconsider its position, and there is now broad agreement that the technology is promising and that facilities should be built in the US and that the initial facilities should be configured with significant research infrastructure. Radiation biologists and radiation physicists at Colorado State University have established active collaborations with colleagues at the NIRS since the 1990s, and this has spurred interest in constructing a heavy ion radiotherapy research and treatment center in Colorado, largely modelled on HIMAC at the NIRS. Our plans comprise four integrated components that leverage strengths at Colorado State University and the University of Colorado, including 1) basic science research rooms for radiobiology, small animal tumor biology, and radiation physics; 2) large (companion) animal translational and clinical research infrastructure, focusing on spontaneous tumors arising in dogs and cats; 3) tumor imaging including a novel isotope research program for PET probe development using small and large animal models; and 4) a human clinical trials program that leverages the strong clinical trials infrastructure at the University of Colorado NCI-designated Comprehensive Cancer Center. The inclusion of large animal research and treatment programs will leverage the world-leading animal cancer program housed in the CSU Flint Animal Cancer Center. There are several advantages of large animal cancer models over traditional rodent models, including the fact that canine and feline tumors arise spontaneously in animals with functional immune systems and thus better model human cancer. Also, techniques that work in large animals, such as tumor imaging, surgery, pharmacokinetics/dynamics, and radiotherapy are readily translated to human clinical practice. Moreover, therapeutic responses to cancer treatments in large animals has greater predictive value of responses in humans. Due to their larger body size, blood draws and biopsies can be performed with dogs and cats at more frequent intervals after a therapeutic intervention than is possible with rodent models, and because of excessive risk, such invasive procedures are not ethical in human patients. Finally, there is a growing appreciation of the value of partnering DVMs with basic scientists and physician scientists to take full advantage of the complementary strengths of these professionals.

We are planning a heavy ion research and treatment facility with the following components. We will construct a flexible beam line to accelerate charged particles from protons to argon (and perhaps as large as iron to allow NASA-funded space radiation studies, an active area of research at CSU). The ion source units will be engineered to allow rapid (seconds to minutes) switching of ions to allow studies of mixed beam radiobiology and tumor biology. There will be three human treatment rooms and a fourth, dedicated large animal treatment room for veterinary patients, all with scanning beam capabilities, and with different arrangements of vertical, horizontal, and angled beam lines. We

will include a shell for a future rotating gantry. Dedicated biology and physics research rooms will be modelled after those at HIMAC and GSI. These components will facilitate integrated basic and clinical programs spanning the full range of research opportunities at the molecular and cellular level, to small and large animal cancer models, and human clinical trials with a broad range of charged particles.

Heavy Ion Radiotherapy Project at Yamagata University Hospital

Kenji Nemoto

Department of Radiation Oncology, Yamagata University School of Medicine, Yamagata, Japan
E-mail: knemoto@ymail.plala.or.jp

Currently, the domestic running facilities are located in Chiba, Hyogo, Gunma and Saga Prefectures, and one facility is under construction in Kanagawa Prefecture. No facility except Yamagata University Hospital is currently planned in northern part of Japan. We believe that we must have one in Tohoku region in order to reduce the medical disparity among the regions, and that we have to complete this construction in about five years.

The basic concept of our facility is “eco-friendly and inside a general hospital”, so we are targeting a compact and energy-saving facilities than ever. We also plan to install a rotating gantry with ten superconducting magnets developed by National Institute of Radiological Sciences. In parallel, we have been establishing a medical IT network system connected to many major hospitals (> 50) in Tohoku region for the on-line case examination.

To successfully maintain carbon therapy facility in northern part of Japan, which has wide landlord and has only a small amount of population less than 10 million, teleconference using TV network will be useful. Using the system, doctors and patients can consult with doctors in carbon ion facility about the indication of the treatment without visiting, because the whole medical records including image data can be shared between the two hospitals. We have started to install this TV conference system to 58 hospitals in Tohoku region and NIRS.

Tohoku Wide Area Particle Therapy Teleconference Participants(58 hospitals)

放射線治療遠隔支援装置 設置先施設リスト		
		2014/05/22現在 58施設
【青森県】 施設数 11施設	【秋田県】 施設数 7施設	【岩手県】 施設数 11施設
① 弘前大学医学部附属病院	① 秋田大学医学部附属病院	① 岩手医科大学
② 青森県立中央病院	② 山本組合総合病院	② 岩大附属PETリニアック先端医療センター
③ 青森市民病院	③ 秋田市立総合病院	③ 盛岡赤十字病院
④ 青森労災病院	④ 大曲厚生医療センター	④ 岩手県立中央病院
⑤ 八戸市民病院	⑤ 由利組合総合病院	⑤ 岩手県立中部病院
⑥ 三沢市立三沢病院	⑥ 秋田厚生医療センター	⑥ 岩手県立二戸病院
⑦ むつ総合病院	⑦ 大館市立総合病院(弘前大学より)	⑦ 岩手県立釜石病院
⑧ つがる総合病院		⑧ 岩手県立胆沢病院
⑨ 八戸赤十字(岩手医科大より)		⑨ 岩手県立磐井病院
⑩ 黒石病院		⑩ 岩手県立大船渡病院(東北大学より)
⑪ 十和田市立中央病院(既設)		⑪ 岩手県立宮古病院
【宮城県】 施設数 11施設	【山形県】 施設数 7施設	【福島県】 施設数 10施設
① 東北大学病院	① 山形大学医学部附属病院(既設)	① 福島県立医科大学附属病院
② みやぎ県南中核病院仙台医療センター	② 山形県立中央病院	② 北福島医療センター
③ 仙台医療センター	③ 山形市立病院済生館	③ 太田西の内病院
④ 仙台総合放射線クリニック	④ 米沢市立病院	④ 白河厚生病院
⑤ 大崎市民病院	⑤ 日本海総合病院(既設)	⑤ 福島労災病院
⑥ 石巻日赤病院	⑥ 鶴岡市立荘内病院(既設)	⑥ 会津中央病院
⑦ 東北労災病院	⑦ 公立置賜総合病院(既設)	⑦ いわき共立病院(東北大学より)
⑧ 仙台市立病院		⑧ 竹田綜合病院(東北大学より)
⑨ 宮城県立がんセンター		⑨ 南東北がん陽子線治療センター(既設)
⑩ 仙台厚生病院(既設)		⑩ 寿泉堂綜合病院(既設)
⑪ 古川星陵病院(確認中)		
【千葉県】 施設数 1施設		
① 重粒子線医科学センター病院(既設)		

Future Plans for Carbon Ion Radiotherapy in Okinawa

Takafumi Toita[1*], Nobumitsu Tamaki[2], Sadayuki Murayama[1]

[1]Department of Radiology, University of the Ryukyu Graduate School of Medical Science, Okinawa, Japan

[2]Okinawa Medical Association, Okinawa, Japan

[*]E-mail: b983255@med.u-ryukyu.ac.jp

Okinawa is an island prefecture located in the southern end of Japan. A project to install a carbon ion radiotherapy facility in Okinawa is currently underway. The Okinawa Medical Association and the Okinawa Prefectural Government are taking the lead with the project under the helpful guidance of the NIRS. The aim of the project is to establish carbon ion radiotherapy as the core cancer treatment in Okinawa and to stimulate medical tourism from Asia and mainland Japan. The facility will have novel scanning beam and rotating gantry port treatment systems. The most important challenge for successful installation of carbon ion radiotherapy in Okinawa is to recruit a sufficient number of medical staff such as radiation oncologists, radiotherapy technologists, and medical physicists.

Recent Status of HIMAC R&D for Next Generation

Koji Noda

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
E-mail: noda_k@nirs.go.jp

Since 1994, NIRS has conducted the HIMAC facility for both the cancer treatment and related studies by heavy-ions. As the beam-delivery method, further, a single beam-wobbling method has been employed, because it is robust toward beam errors and offers easy dose management. The protocols were significantly increased after the development of the respiratory-gated irradiation. In 2003, the Japanese government approved the carbon-ion RT with HIMAC as a highly advanced medical technology. Just after this approval, NIRS proposed a standard carbon-ion RT facility [3] in order to boost the carbon-ion RT in Japan through the reduction of the construction cost by downsizing the facility size. The fruits of this work were realized as a pilot facility in Gunma university Hospital Medical Center (GHMC), which has been successfully conducted since 2010.

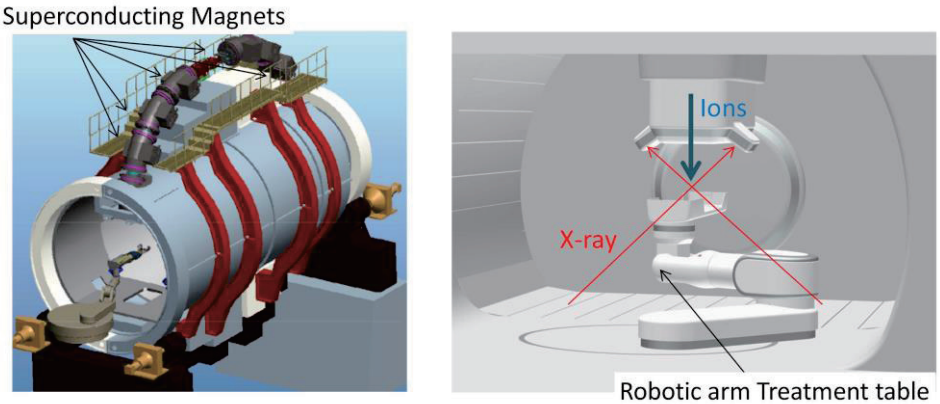
Since 2006, further, NIRS has been engaged in a “new treatment research project” toward a new next generation research. One of the most important purposes is to realize the “adaptive cancer radiotherapy” to accurately treat tumor even with changing both the tumor size and shapes during a treatment period. Since both the static and moving tumors should be treated in NIRS-HIMAC, The phase-controlled rescanning (PCR) method, based on a fast 3D scanning technology with a pencil-beam scanning, has been developed to move toward the goal of adaptive cancer radiotherapy. In order to verify the developed technology through the clinical study, the new treatment research facility was constructed. As the first stage, one of three treatment rooms has been opened since May 2011, utilizing an energy degrader for slice change for depth scanning in the 3D scanning. As the second stage since September 2012, both the first and second rooms have been being operated with the hybrid depth scanning with eleven energy steps of the HIMAC synchrotron toward more accurately treatment. The NIRS scanning will adapt a full depth scanning with 201 energy steps of the HIMAC synchrotron from 2015. Until July 2014, operating two treatment rooms treated patients of around 550 even under 3 hours operation a day. In 2015, further, since a treatment of moving target with the PCR method is scheduled in the new treatment research facility. As the third stage, a compact carbon-ion rotating gantry has been developed in order to realize the intensity modulated carbon-ion RT (IMCT) combined with the 3D scanning, which will bring the more accurate and shorter-course treatments owing to the higher dose concentration. This rotating gantry will be installed to the third room and its commissioning will be started in 2015.

Development on Rotating Gantry with Superconducting Magnets

Toshiyuki Shirai[1*], Takashi Fujita[1], Takuji Furukawa[1], Yousuke Hara[1], Yoshiyuki Iwata[1], Kentaro Miki[1], Kota Mizushima[1], Shinichiro Mori[1], Takeshi Murakami[1], Naoya Saotome[1], Shinji Satou[1], Yuichi Saraya[1], Kouichi Shouda[1], Shinji Suzuki[1], Ryohei Tansho[1], Yukio Yoshiwara[1], Koji Noda[1], Tetsuya Fujimoto[2], Toru Ogitsu[3], Tetsuhiro Obana[4], Naoyuki Amemiya[5], Tomofumi Orikasa[6], Shigeki Takayama[6]

[1]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
[2]Accelerator Engineering Corporation (AEC), Chiba, Japan
[3]High Energy Accelerator Research Organization (KEK), Ibaraki, Japan
[4]National Institute for Fusion Science (NIFS), Gifu, Japan
[5]Faculty of Engineering, Kyoto University, Kyoto, Japan
[6]Toshiba Corporation, Tokyo, Japan
[*]E-mail: t_shirai@nirs.go.jp

A rotating gantry is an attractive tool for radiotherapy, because targets are irradiated from desirable directions. However, it is difficult to realize it for carbon ion radiotherapy due to the high magnetic rigidity of beams. Facilities are equipped with fixed-irradiation ports and rotation or rolling of a treatment table has been used to optimize irradiation directions. The world's first rotating gantry for carbon ion radiotherapy was constructed at HIT in Heidelberg University and the length and the radius are reported to be 25 m and 6.5 m, respectively, while the typical dimensions of proton gantries are 10 m in length and 5m in radius. The design of a compact isocentric rotating gantry was started at 2011 in NIRS and combined-function superconducting magnets have been developed as a key issue. The length and radius of the gantry become 13 and 5.5 m, respectively. The fast 3D scanning irradiation system, the markerless X-ray respiratory gating system and the robotic arm treatment table are available in the gantry treatment room. The installation of the rotating gantry is scheduled in January 2015 at NIRS and the beam commissioning will be started in the autumn of 2015.



Design of the rotating gantry (left) and the treatment room (right)

Recent Status of GSI/Heidelberg R&D for Next Generation

Thomas Haberer

Heidelberg Ion-Beam Therapy Center (HIT), Germany

E-mail: Thomas.Haberer@med.uni-heidelberg.de

Status of Biological Treatment Planning at HIT with the Local Effect Model (LEM)

Oliver Jäkel

German Cancer Research Center (DKFZ), Germany
and
Heidelberg Ion Beam Therapy Center, Germany
E-mail: o.jaekel@dkfz.de

Carbon ion radiotherapy started in Germany within a pilot project at the national heavy ion research laboratory GSI as a cooperative project between GSI, the University Hospital Heidelberg, the German Cancer Research Center and the Research Center Dresden-Rossendorf. Between 1997 and 2008 435 patients have been treated with a scanned carbon ion beam. In order to allow for a biologically optimized treatment planning, the local effect model was developed at GSI [1]. The model relies on the assumption that the local effect of a dose deposited within the structures of the cell is intrinsically always the same for all radiation modalities. Differences in the biological effect for different modalities arise due to the very different microscopic patterns of dose distribution between low and high LET radiation. Hence a track structure model is needed for description of the microscopic dose. If the biological and clinical effects arising from X-rays are known, the LEM model predicts the corresponding effects for a mixed field of ions, like carbon in clinical applications. In clinical practice that means, that basically the α and β values for the clinical endpoint under consideration have to be known, in order to predict the RBE of a mixed radiation field. The LEM model was adopted also for the treatment planning at the Heidelberg Ion Beam Therapy Center (HIT) at the University Hospital Heidelberg which started operation in 2009 and where more than 2500 patients received treatment until late 2014. The LEM model has been benchmarked by several large in-vivo animal studies [2] and consequently undergone several modifications. In this contribution, the clinical application of the model is discussed and some recent findings derived from clinical endpoints [3] are discussed.

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Biological Models for Carbon-Ion Radiotherapy at NIRS

Naruhiro Matsufuji*, Taku Inaniwa and Nobuyuki Kanematsu

Medical Physics Research Program, Research Center for Charged Particle Therapy
National Institute of Radiological Sciences (NIRS)
*E-mail: matufuji@nirs.go.jp

It is a requisite in treatment planning system (TPS) for the successful ion beam therapy to understand and control the changing relative biological effectiveness (RBE) of the beam in the irradiation field. Under limited information available for the RBE of the carbon-ion beam, we established a pragmatic RBE model [1] in initiating carbon ion radiotherapy with broad-beam irradiation technique in 1994. In this original model the dose distribution of therapeutic carbon-ion beams was designed based on representative *in-vitro* Human Salivary Gland (HSG) cell survival response. The HSG response was scaled to clinical response by making use of biological and clinical response for another high-LET radiation, fast neutron. The resultant RBE distribution was simply dependent on the irradiation depth and thus useful in reducing the number of parameters in the analysis of the clinical results. The clinical RBE observed in terms of tumour control probability (TCP) were found to show good agreement with the model expectation [2] which supports the accurate RBE estimation with the original model.

The biological model was updated in 2011 when new scanning irradiation method was introduced. The new model was expected to improve approximation introduced in the original model in order to make maximum advantage of the flexibility of the scanning irradiation method. At the same time is was strongly necessary for the new model to harmonize with the original model in order to make maximum advantage of the excellent clinical outcomes achieved under the original model.

Under these requirements, we have successfully developed the new model, MKM2010 [3]. MKM2010 is based on Microdosimetric Kinetic Model (MKM) [4] and upgraded to be applicable for high-LET radiation. MKM2010 versatilely estimates the RBE as a function of time at any point even in highly complex irradiation field with microscopic spatial energy information as a physical input. Because the physical information can be derived experimentally and/or theoretically, MKM2010 is also useful in understanding the mechanism of RBE for various therapeutic radiations.

As shown in the figure, it has been confirmed that MKM2010 enables highly accurate and precise estimation on RBE. In order to retain the continuity, the resultant dose by MKM2010 was harmonized with that by original model at the center of the target. Now MKM2010 has been utilized for ongoing carbon ion radiotherapy at NIRS in TPSs for both broad-beam and scanning irradiation.

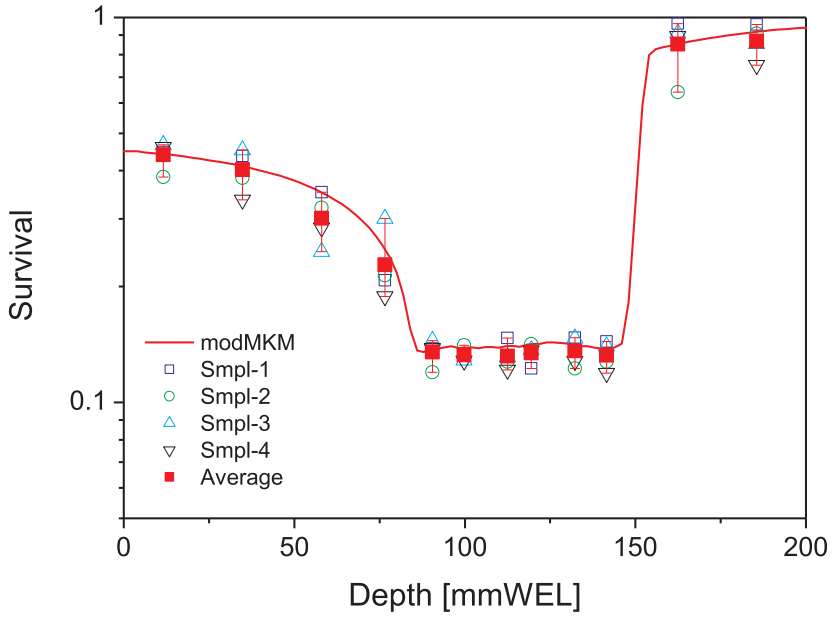

Figure Experimental HSG cellular survival for carbon 290 MeV/n beam (60mm SOBP) with prediction by MKM2010 (line).

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Dept. of Planning and Management
National Institute of Radiological Sciences
Anagawa 4-9-1, Inage-ku, Chiba, 263-8555, Japan
Tel: +81-43-206-3025 Fax: +81-43-206-4061
E-mail: kokusai@nirs.go.jp
http://www.nirs.go.jp/ENG/index.html

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