Proceedings of

10th Heavy Ion Charged Particle Therapy Symposium

International Symposium on

Heavy Ion Radiotherapy and Advanced Technology

January 12 - 13, 2011 (Wed - Thu)

Organized by

National Institute of Radiological Sciences

Venue

Hitotsubashi Memorial Hall, Tokyo, Japan

Foreword

In the 30-plus years since it began its fast neutron radiotherapy in 1975, the National Institute of Radiological Sciences (NIRS) has pursued extensive research on cancer radiotherapies that utilize proton and heavy ion (carbon) beams. In particular, NIRS has already treated close to 6,000 patients with the heavy ion cancer radiotherapies which it began providing in 1994 as an integral element of the nation's first comprehensive 10-year strategy against cancer, and in the process has demonstrated success in developing new radiotherapies that facilitate highly improved dose concentrations and radiobiological effectiveness.

Drawing from an amassed wealth of clinical research accomplishment, currently NIRS is engaged in efforts to promote the broader acceptance and utilization of heavy ion radiotherapies in Japan and overseas, encourage the sharing of clinical data through the creation of an international heavy ion radiotherapy network, and pursue undertakings in more advanced research and development.

Through this symposium, we plan to present not only the clinical findings of NIRS heavy ion radiotherapy performed to date but also the recent accomplishments of and future prospects for radiobiological studies as well as physical engineering-related research focused on the development of new medical tools and instrumentation. Additionally, we have invited researchers from other heavy ion radiotherapy facilities worldwide to attend and deliver papers on the latest developments in their clinical research and radiotherapy instrumentation as well as give presentations on plans of virtually all new radiotherapy facilities currently under construction or in the study stages. We accordingly believe the symposium will serve as an excellent opportunity to promote deeper understanding of trends in the heavy ion radiotherapy field. The end of this document contains a list with short profiles of these radiotherapy tools and facilities.

NIRS is committed to ongoing fundamental research and clinical studies aimed at ensuring that all patients have access to more powerful as well as gentle forms of radiotherapy whenever and wherever the need arises. Our hope is that the opportunities afforded by this symposium will lead to broader understanding of and support for that quest.

Tadashi Kamada
Research Center for Charged Particle Therapy
National Institute of Radiological Sciences

National Institute of Radiological Sciences
10th Heavy Ion Charged Particle Therapy Symposium
International Symposium on Heavy Ion Radiotherapy and Advanced Technology

Venue: Hitotsubashi Memorial Hall Academic Center
Date: 12-13 January, 2011
Admission: Free

January 12 (Wed.)

9:00	-	9:30	(30)	*Registration*		
9:30	-	9:40	(10)	Opening Remarks	Y. Yonekura	(NIRS)
9:40	-	9:50	(10)	Greetings		
				Outline of heavy ion radiotherapy		
9:50	-	10:10	(20)	Heavy Ion Radiotherapy: Yesterday, Today and Tomorrow	William Chu	(LBNL.)
10:10	-	10:30	(20)	Radiological Background of Heavy Ion Cancer Therapy	Marco Durante	(GSI)
10:30	-	10:50	(20)	History and Advance of Various Particle Therapies	Hirohiko Tsujii	(NIRS)
10:50	-	11:10	(20)	*Break*		
				Clinical experience at NIRS (1)		
11:10	-	11:25	(15)	Bone and Soft-tissue Tumors	Reiko Imai	(NIRS)
11:25	-	11:40	(15)	Lung Cancer	Naoyoshi Yamamoto	(NIRS)
11:40	-	11:55	(15)	Locally Reucurrent Rectal Cancer	Shigeru Yamada	(NIRS)
11:55	-	12:10	(15)	Prostate Cancer	Hiroshi Tsuji	(NIRS)
12:10	-	13:35	(85)	*Lunch*		
				Clinical experience at the present facilities		
13:35	-	13:55	(20)	Clinical Experience of Carbon Ion Radiotherapy at GSI/Heidelberg	Juergen Debus	(HIT)
13:55	-	14:10	(15)	Clinical Experience of Carbon Ion Radiotherapy at Hyogo	Masao Murakami	(Hyogo Ion Beam C.)
14:10	-	14:25	(15)	Clinical Trial of Tumor Therapy with Carbon Ions at Heavy Ion Research Facility in Lanzhou (HIRFL), IMP, China	Hong Zhang	(IMP)
14:25	-	14:40	(15)	Carbon Ion Radiotherapy at Gunma University	Takashi Nakano	(Gunma Univ.)
14:40	-	15:00	(20)	*Break*		
				Status of Facilities under Construction		
15:00	-	15:15	(15)	Current Status of CNAO	Junetsu Mizoe	(CNAO)
15:15	-	15:30	(15)	Status of the ETOILE Center at the End of 2010	Jacques Balosso	(ETOILE)
15:30	-	15:45	(15)	Particle Therapy Center Marburg, A Combined Proton - Carbon Ion Treatment Facility Status Report	Rita Engenhart-Cabillic	(Univ. of Marburg)
15:45	-	16:00	(15)	SAGA-HIMAT (Heavy Ion Medical Accelerator in Tosu) - The First Japanese Heavy Ion Therapy Facility Constructed and Operated by Public-Private Partnership	Tadahide Totoki	(Saga-HIMAT)
16:00	-	16:15	(15)	Current Status of MedAustron	Ramona Mayer	(Med Austron)
16:15	-	16:30	(15)	NRoCK - Status Report	Ralf Kampf	(Univ. Kiel-SH)
16:30	-	16:45	(15)	Introduction of Shanghai Particle Therapy Center	Guo-Liang Jiang	(Fudan Univ.)
				Special Lecture		
16:45	-	17:10	(25)	The San Francisco Bay Area Particle Accelerator Research Center (SPARC): a Collaborative Effort between Stanford/SLAC & LBNL/UCSF	Mack Roach	(UCSF)

January 13 (Thu.)

Clinical experience at NIRS (2)

9:00	-	9:15	(15)	Skull Base and Head-and-Neck Tumors	Azusa Hasegawa	(NIRS)
9:15	-	9:30	(15)	Hepatocellular Carcinoma	Shigeo Yasuda	(NIRS)
9:30	-	9:45	(15)	Locally Advanced Cervical Cancer	Shingo Kato	(NIRS)
9:45	-	10:00	(15)	Pancreatic Cancer	Makoto Shinoto	(NIRS)
10:00	-	10:20	(20)	What's Next in Carbon Ion Radiotherapy at NIRS?	Tadashi Kamada	(NIRS)
10:20	-	10:40	(20)	*Break*		

Future Prospects

10:40	-	11:00	(20)	Future Trends in European Radiation Oncology and Ion Beam Therapy	Jean Bourhis	(Inst. Gustave Roussy)
11:00	-	11:15	(15)	KIRAMS project: New Challenges from CyberKnife to Heavy Ion Radiotherapy	Chul-Koo Cho	(KIRAMS)
11:15	-	11:30	(15)	Mayo Clinic Charged Particle Cancer Treatment Program	Robert Foote	(Mayo Clinic)
11:30	-	11:45	(15)	Prefectural Plan to Install a Heavy Charged Particle Radiotherapy System at Kanagawa Cancer Center: a progress Report	Yuko Nakayama	(Kanagawa Cancer C.)
11:45	-	12:00	(15)	Future Plan of Heavy Ion Radiotherapy in Taiwan	Cheng-Yen Chang	(Taipei Veterans General H.)
12:00	-	12:15	(15)	Future Plan of Heavy Ion Radiotherapy in Malaysia	Wan Kamil	(USM)
12:15	-	12:30	(15)	Future Plan of Heavy Ion Radiotherapy in Saudi Arabia	Belal Moftah	(KFSH & RC)
12:30	-	13:40	(70)	*Lunch*		

Expected Benefit and Efficiency of Treatment

13:40	-	13:55	(15)	Expected Benefit and Efficiency of Treatment: CNAO Approach	Roberto Orecchia	(CNAO)
13:55	-	14:10	(15)	Cost Effectiveness of Carbon Ion Radiotherapy: Comparison with Other Treatments	Tatsuya Ohno	(Gunma Univ.)
14:10	-	14:30	(20)	Medical Tourism in Heavy Ion Radiotherapy	Koichi Kawabuchi	(Tokyo M&D Univ.)
14:30	-	14:50	(20)	*Break*		

Developments at NIRS

14:50	-	15:10	(20)	Dvelopment of Heavy-Ion Radiotherapy Technology in NIRS	Koji Noda	(NIRS)
15:10	-	15:25	(15)	Development of the Treatment Planning system for Spot Scanning Carbon Ion Therapy	Naruhiro Matsufuji	(NIRS)
15:25	-	15:40	(15)	Next-generation Irradiation System at New Particle Therapy Research Facility in NIRS	Toshiyuki Shirai	(NIRS)
15:40	-	15:55	(15)	Recent Advances in biological Experiments for Heavy-ion Radiotherapy	Ryuichi Okayasu	(NIRS)
15:55	-	16:00	(5)	Closing Remarks	Hirohiko Tsujii	(NIRS)

January 14 (Thu.)

14:20	-	16:20		Site tour: New particle-therapy research facilities	at NIRS

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http://www.nirs.go.jp/news/event/2011/01_12.shtml (Japanese)
http://www.nirs.go.jp/ENG/info/110112.shtml

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Appendix

DAY 1 : Wednesday, 12 January

Heavy Ion Radiotherapy: Yesterday, Today and Tomorrow*

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Abstract

At EO Lawrence Berkeley National Laboratory (LBNL), clinical trials were conducted (1975-1992) for treating human cancer using heavy ion beams, in which about 700 patients were treated with helium-ion and about 300 patients with neon-ion beams. Clinical trials at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany used carbon-ion beams to treat about 250 patients (1997-2005). In 1993 the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, commissioned its first-in-the-world medically-dedicated Heavy Ion Medical Accelerator in Chiba (HIMAC), which accelerates heavy ions to an energy of 800 MeV/u (million electron volts per nucleon). By 2010 more than 5000 patients have been treated using carbon-ion beams at HIMAC. Following its successful clinical operation, several carbon-ion therapy facilities have been, or will be soon, constructed in: Hyogo (commissioned in 2001) and Gunma (2010), Japan; Heidelberg (2009), Marburg (2010) and Kiel (2012), Germany; Pavia (2010), Italy; Lyon (2015), France; Wiener Neustadt (2015), Austria; Shanghai (2015) and Lanzhou, China; and Busan (2016), Korea. Very active clinical research and technology development projects are carried out at these institutions to enhance beam delivery accuracy, such as beam scanning that compensates for organ movements, which will further improve the clinical efficacy of the ion-beam therapy in the future.

Introduction

In 1895, Wilhelm Conrad Röntgen produced X-rays, which are short-wave electromagnetic radiations that readily penetrate human body. Soon it was recognized that the energy that does not pass through the body would be deposited within it and it is this energy that causes the biological effects of radiation in tissue, such as killing cancer cells. Within two months of their discovery, X-rays were used both in Europe and North America not just to take pictures of the internal organs of living people but also to treat a wide variety of diseases, including malignant tumors [1]. As we know now, an X-ray beam is made up of energetic photons, which loses its intensity while penetrating human body. Therefore, in treating deep-seated tumors, photon-beams are bound to deposit higher dose upstream of the target volume, and also significant dose in its downstream regions (see the photon curve in Fig. 1). Nevertheless, photon beams are the most widely used cancer treatment modality today. Modern day radiation treatments of cancer employ linear accelerators (linacs) that accelerate electrons to tens of MeV before they bombard target materials to produce high-energy photon beams. The beam delivery method, called Intensity Modulated Radiation Therapy (IMRT), delivers photon beams aiming the target from many different directions, thereby dilutes unwanted doses outside the treatment volume. These photon beam treatments are often called "conventional" radiotherapy to distinguish them from the new proton and heavier ion-beam treatments that are discussed below.

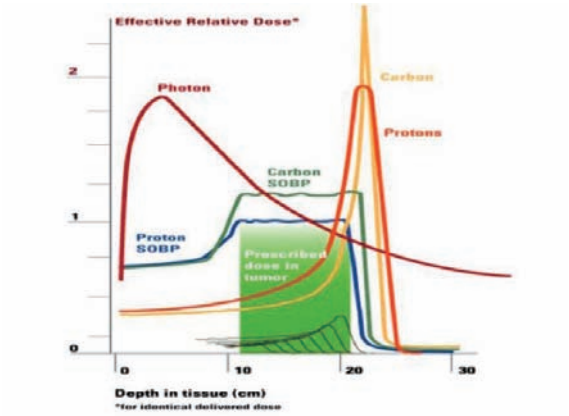

Fig. 1: The relative dose of a photon beam as a function of penetrating depth in water is shown as a reference radiation. The Bragg peaks of proton and carbon-ion beams are also shown. To cover the extended target volume, the energy of particle beam is modulated to adjust the depth of Bragg peak to form a Spread-Out Bragg Peak (SOBP). The relative depth doses of the SOBP of proton and carbon ion beams are compared with that of a photon beam. The doses are normalized to the dose at the entrance to the body. For equal target dose, carbon beams exhibit the lowest entrance dose among the three beams.

In 1948, Prof. Ernest Orlando Lawrence completed construction of the 184-inch Synchrocyclotron at the University of California (UC) Berkeley, making it possible to accelerate protons, deuterons and helium nuclei to energies of several hundred MeV/u. Note that protons and heavier ions are much more massive than electrons, and consequently it requires much bigger accelerators to accelerate them to acquire enough kinetic energy to reach deep-seated tumors in human body. For example, a proton is 1836 times more massive than an electron. Energetic ion beam deposits much of its energy at the end of the range, resulting in what is called Bragg peak (Fig. 1), so named after the Australian physicist Sir William Henry Bragg who discovered the phenomenon [2]. Realizing the advantages of delivering a larger dose in the Bragg peak when placed inside deep-seated tumors, Prof. Robert Wilson at Harvard University published his seminal paper on the rationale of using accelerated protons and heavier ions for treatment of human cancer [3]. Compared to conventional photon treatments, these particle beams promised higher cure rates with fewer complications, as they would deliver tumor-killing doses more precisely, while lowering unwanted doses to normal tissues adjacent to the treatment volume. In 1952, Professors Cornelius A. Tobias and John H. Lawrence at UC Berkeley performed the first therapeutic exposure of human patients to ion (deuteron and helium ion) beams [4].

Soon after, programs of proton radiation treatments had opened in proton accelerators, which were originally constructed for nuclear physics research, in: Uppsala, Sweden (1957), Cambridge, Massachusetts (1961), Dubna (1967), Moscow (1969) and St Petersburg (1975) in Russia, Chiba (1979) and Tsukuba (1983) in Japan, and Villigen, Switzerland (1984) [5]. The first hospital-based proton facility was commissioned at the Loma Linda University Medical Center in California in 1990 [6]; and now about 30 industry-built proton therapy facilities became operational around the world.

Heavier Ions for Cancer Treatment

Early Clinical Trials Using Heavy Ions

In the 1950s, LBNL constructed the Bevatron, a 6 giga-electron-volts (GeV) synchrotron, which by the early 1970s accelerated ions with atomic numbers between 6 and 18, to energies that permitted the initiation

of radiological physics and biological studies [7]. In the 1970s LBNL established the Bevalac accelerator complex, in which the SuperHILAC (Heavy Ion Linac) was used to inject heavier ion beams into the Bevatron for acceleration to energies up to 2.1 GeV per nucleon. The Bevalac, by producing high intensities of protons and other heavier ions with sufficient energy to penetrate the human body, expanded the opportunity for medical studies for treatment of deep-seated cancers [8].

Ion beams combine superior physical and biological characteristics for effective cancer therapy. In penetrating human body, compared with proton beams, ion beams scatter less and exhibit smaller energy straggling resulting in steeper distal dose falloffs. These mean that the widths of fuzzy boundaries of radiation fields (called penumbrae) are much narrower for ion beams when compared with those for photon or proton beams. As ion beams could more accurately delineate target volumes sitting adjacent to critical organs than photon or proton beams could, higher ion-beam dose may be delivered into the target volumes. Clinical expectation is higher tumor control with a lower normal tissue complication probability.

In penetrating human body, heavier ion beams show higher “linear energy transfer” (LET), which stands for the radiation energy deposited per unit length in tissue. X-rays and proton beams are low-LET radiations that produce mostly single-strand breaks in irradiated DNA molecules inside the cells. Single-strand breaks are often repaired, resulting in recurrence of tumors. Whereas heavier ion beams, with high-LET radiation in Bragg peaks, produce double-strand beaks in DNA molecules. Double-strand breaks cannot be repaired and therefore the outcome results in lower recurrence of tumors (Fig. 2). Heavier ion beams have clinically demonstrated their superior tumor eradicating ability with lower complication and recurrence probability.

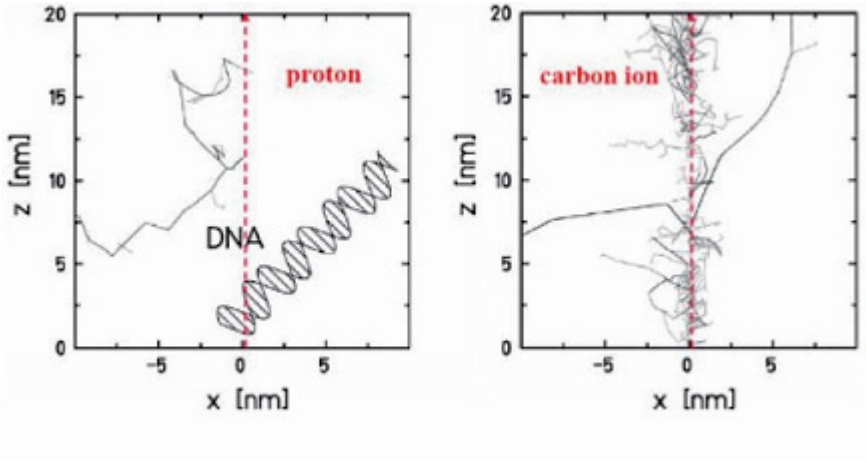

Fig. 2. The structure of a proton and a carbon track in nanometre resolution are compared with a schematic representation of a DNA molecule. The higher density of the secondary electrons, produced by carbon ions, creates a large amount of clustered DNA damage.

From 1975 to 1992, Prof. Joseph R. Castro and his team from UC San Francisco conducted clinical trials for treating human cancer using the spread-out Bragg peak of helium ion beams at the 184-inch Synchrocyclotron and heavier ion beams at the Bevalac [9]. Ions of interest ranged from ^{4}He to ^{28}Si; whereas, ^{20}Ne was the most commonly used ions. The numbers of patients treated under US national protocols (NCOG/RTOG) were ~700 patients with helium-ion beams and ~300 patients with neon-ion beams. The patients treated with helium ions included primary skull-base tumors: chondrosarcomas, chordomas, meningiomas, etc. Using ^{20}Ne ions, they also treated, and obtained excellent 5-year local

control of lesions arising from paranasal sinuses, nasopharynx or salivary glands, and extending into the skull base.

Carbon Ions vs. Protons

The therapeutic advantage of carbon ions versus protons stems from three decisively superior characteristics of the former:

(i) Compared with proton beams, carbon-ion beams produce higher dose conformation to the tumor volume (Fig. 3). Sparing of the surrounding healthy tissues from unwanted radiation is increased, therefore higher therapeutic doses can be placed in the tumor, producing higher cure rates with fewer complications.

(ii) Many recurrences of tumors following radiation treatment come from the re-growth of hypoxic tumor cells (cells that have "outgrown" their blood supply and are thus oxygen starved). They are radioresistant to X-rays and protons. Carbon ion beams, which have higher LET, are more efficient in killing anoxic tumor cells and significantly lower the chance of tumor recurrence.

(iii) Proton-beam treatments are usually delivered 4 or 5 times per week over 7-8 weeks (in 28-40 fractions). Safe and effective carbon-ion beam treatments are delivered in fewer fraction numbers, such as 8-12; and possibly even fewer for some tumor sites, perhaps as low as 1-4 fractions [10]. This allows higher patient throughput in an ion-beam facility, which lowers the cost of treatments and enhances patient comfort.

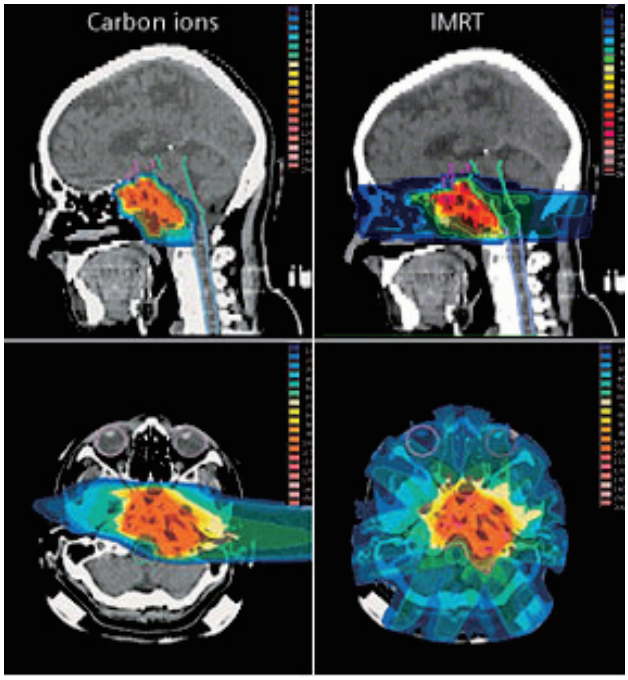

Fig. 3: Left panels show a therapy plan for treating a head-and-neck tumor using one carbon ion beam. For comparison, right panels show a therapy plan for treating the same tumor using most advanced photon treatment, IMRT that employs multiple beams. (Based on a publication of Heidelberg Univ., Dept. Clinical Radiology and German Cancer Research Center.)

Therapy plans for carbon-ion beam and photon beam treatments are shown in Fig. 3, which demonstrates the superiority of single beam of carbon-ions over the most advanced Intensity Modulated Radiation Therapy (IMRT) using multiple photon beams.

As high-dose 3D-conformal treatment has become the clearly accepted objective of radiation oncology, clinical trials using proton and carbon-ion beams are concurrently and methodically pursued. Protons with relatively low values of LET have been demonstrated to be beneficial for high-dose local treatment of many of solid tumors, and have reached a high degree of general acceptance after more than six decades of treating over 70,000 patients by the end of 2010. However, some 15% to 20% of tumor types have shown resistant to even the most high-dose low-LET irradiation. For these radio-resistant tumors, treatment with carbon ions offers great potential benefit. These high-LET particles offer the unique combination of excellent 3D-dose distribution and increased LET values, to eradicate tumor cells while reducing the effects of unwanted radiation in adjacent healthy tissues [10].

Current Status of Ion-Beam Therapy Facilities

In 1994 the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, under the leadership of Prof. Yasuo Hirao, commissioned the Heavy Ion Medical Accelerator in Chiba (HIMAC), which has two synchrotrons and produces ion beams from H to Xe up to a maximum energy of 800 MeV/u (at q/m=1/2) (Fig. 4) [11].

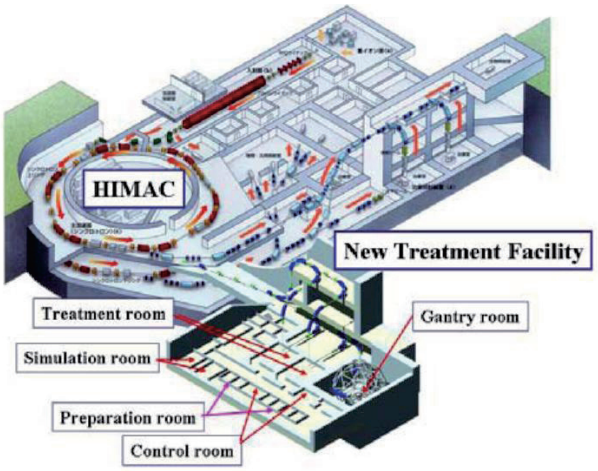

Fig. 4: Schematic view of HIMAC. The lower part depicts the new treatment facility addition (2011). (K. Noda, NIRS)

The HIMAC serves three treatment rooms, one with both a horizontal and a vertical beam, and the others with a horizontal or vertical beam only. There are also a secondary (radioactive) beam room, a biology experimental room, and a physics experimental room, all equipped with horizontal beam lines. As of February 2010, Prof. Hirohiko Tsujii and his staff have treated a total of 5,189 patients. Clinical results have shown that carbon-ion treatments have the potential ability to provide sufficient dose to the tumor, together with acceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to carbon ions include locally advanced tumors as well as those with histologically non-squamous cell type of tumors, such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. By taking advantage of the unique properties of carbon ions, Prof. Tsujii successfully carried out treatments with a large dose per fraction within a short treatment period for a variety of tumors [10]. At GSI, Darmstadt, Germany, Prof. Dr. Jürgen Debus and his group of Heidelberg University conducted clinical trials using carbon-ion beams [12]. A comparison of clinical results from photon and carbon-ion radiotherapy for selected tumor sites is shown in Table 1. This list clearly demonstrates the superior clinical efficacy of carbon ion beams over photon beam treatments. The clinical results are based on the Table compiled by Prof. Gelhard Kraft [13], which is updated by Yamada et al. [14].

		Photons	Carbon Ion	
Indication	End point		NIRS-HIMAC	GSI
Chordomas	Local control rate	30-50%	95% (5y)	70%
Chondrosarcomas	Local control rate	33%	100% (5y)	89%
Nasopharynx carcinoma	5 year survival	40-50%	61%	
Glio-blastoma	Av. survival time	12 months	16 months	
Choroid melanoma	Local control rate	95%	96%	
Paranasal sinus tumors	Local control rate	21%	70% 5y	
Adenoid cystic carcinoma	5 year survival	57%	72% (5y LC 81%)	
Pancreatic carcinoma	Av. survival time	6.5 months	21 months	
Liver tumors	5 year survival	23%	33%	
Recurrent Rectal cancer	5 year survival	0-16%	45%	
Salivary gland tumors	Local control rate	24-28%	81%(5y)	77.5%
Soft-tissue sarcoma	5 year survival	31-75%	52-83%	

Table 1. *Comparison of clinical results of photon and carbon-ion treatments of selected tumor sites.*

In 2001, the Hyogo Ion Beam Medical Centre (HIBMC) was commissioned at Harima Science Garden City, Japan, which provided for the firs time both proton and carbon-ion beams for clinical use in one facility. The third carbon-ion therapy facility in Japan was commissioned at the Gunma University Heavy Ion Medical Center (GHMC), where its first patient was treated in March 2010.

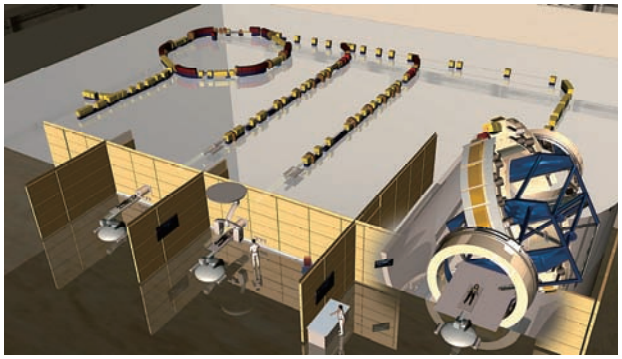

Fig. 4: Schematic view of HIT at Heidelberg, Germany.

At the Heidelberg Ion Beam Therapy Centre (HIT), as shown in Fig. 4, two ion sources feed the synchrotron via a linear accelerator. It houses three treatment rooms: two with a horizontal beam and one with a rotating gantry, which makes it possible to aim the beam at the patient from all directions. This system, which will be capable of treating tumors with both carbon ions and protons, was commissioned in 2009 [15]. A second and third carbon-ion and proton beam therapy centers in Germany are under construction at the Klinikum Geisse-Marburg in Marburg (Particle Therapy Center (PTZ), 2010) and North European Radiooncological Center Kiel (NroCK) in Kiel.

The Centro Nazionale di Adroterapia Oncologica (CNAO) will commission a carbon-ion beam treatment facility in Pavia, near Milan, Italy in 2010. The facility will provide proton and carbon-ion beams with maximum energy of 400 MeV/u [16].

Under the leadership of Prof. Hirohiko Tsujii, NIRS has been very active in promoting carbon-ion therapy around the world. NIRS has organized numerous joint symposiums, for example:

- NIRS-IMP Joint Symposium on Carbon Ion Therapy, August 14-15, 2009, Institute of Modern Physics, Lanzhou,

China.

- NIRS-CNAO Joint Symposium on Carbon Ion Radiotherapy, March 20-21, 2010, Pavia, Italy.
- Japanese-European Joint Symposium on Ion Cancer Therapy, and NIRS-KI Joint Symposium on Ion-Radiation Sciences, September 9 & 10-11, 2010, Stockholm, Sweden.

To summarize, the current worldwide situation with carbon-ion therapy facilities, which are operating, under construction, and in planning stages are:

- Japan: in Chiba (HIMAC, commissioned in 1994), Hyogo (HIBMC, 2001) and Gunma (GHMC, 2010), Tosu city in Saga Prefecture (SAGA Heavy Ion Medical Accelerator in Tosu (H IMAT)) and Yokohama city in Kanagawa Prefecture (Kanagawa Cancer Center)
- Germany: in Heidelberg (HIT, 2009), Marburg (PTZ, 2010), Kiel (NroCK, 2012), Aachen and Berlin
- Italy: in Pavia (CNAO, 2010) and Catania
- France: in Lyon (Centre Etoile, 2015), Caen (Asclepios [17])
- Austria: in Wiener Neustadt (MedAustron, 2015)
- China: in Shanghai (Shanghai Proton & Heavy Ion Hospital, 2015) and Lanzhou (Institute of Modern Physics)
- Korea: in Busan (DIRAMS, 2016)
- USA: in Minnesota and California

In contrast to the fact that almost all ion-beam facilities discussed here uses a synchrotron, Ion Beam Associate (IBA) of Belgium proposes to use a superconducting isochronous cyclotron, with an ECR source, 25 keV/Z axial injection, to accelerate helium and carbon ions to 400 MeV/u and protons to 260 MeV [17].

Very active clinical research and technology development projects are carried out at various carbon-ion therapy centers to enhance beam delivery accuracy. New beam delivery techniques will use beam scanning to conform the Bragg peak dose to irregularly shaped treatment volumes. When such dynamic beam delivery methods are used, one must compensates for organ movements during the beam delivery with beam scanning. Various techniques considered include: (i) beam gating that delivers radiation only during the selected physiological phases, such as in respiration-gated beam delivery, or (ii) beam tracking the organ movements. Improved beam delivery will further improve the clinical efficacy of the ion-beam therapy in the future. HIMAC is completing its expansion to be completed in the spring of 2011 (Fig. 4), where a beam scanning will be implemented for treatment delivery [18].

Concluding Remarks

Each year in the United States, nearly one million patients are treated with radiation therapy, and at least 75 percent of these patients are treated with the intent to cure the cancer, rather than control the growth or relieve symptoms including pain [19]. Clinical experience suggests that at least 10% of these patients would benefit significantly from treatment with therapeutic beams of carbon ions, in place of conventional megavoltage X-ray or proton treatments. It follows that one may perform parallel epidemiological analyses for the Japanese population, and arrive at similar conclusions.

This potential benefit of carbon-ion beam therapy arises from two important properties, which together are uniquely characteristic of accelerated carbon ions: (i) the ability to locally deliver high tumor-killing doses of radiation to tumor sites deep within the body, while sparing surrounding critical tissues from harmful radiation, and thereby increase the likelihood of cure with fewer complications [20], and (ii) the effectiveness of carbon-ion radiation in killing tumor cells that are resistant to photon or proton-beam radiation, thereby reducing the incidence of local failures of treatment.

There are now five carbon-ion therapy facilities operating in the world, and more are under construction or in planning stages; however, most of them are in developed countries. For the welfare of mankind everywhere, it is hoped that ion-beam therapy facilities should become more universally available. To accomplish this objective, we need development of technologies in accelerating and delivering ion beams more effectively, safely and economically. The future ion-beam therapy facility developers should remember that operation of a complex facility in a clinical environment requires conservative and simple designs that can be operated and maintained by a non-specialist staff to produce reliable and

consistent performance, even with gradual subsystems degradation with the usage of the facility.

Acknowledgment

Work supported by the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

References

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Radiological Background of Heavy Ion Cancer Therapy

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Abstract

Densely ionizing radiation, such as heavy ions, produce biological damage which is different from that normally produced by sparsely ionizing radiation, such as X- or γ-rays which are a large component of the natural radiation background. In fact, as a result of the different spatial distribution of the energy deposited, along the core and penumbra of the track, DNA lesions are exquisitely complex, and difficult to repair. RBE factors are normally used to scale from X-ray to heavy ion damage, but it should be kept in mind that RBE depends on several factors (dose, dose rate, endpoint, particle energy and charge, etc.) and sometimes heavy ions produce special damages that just cannot be scaled from X-ray damage. The special characteristics of heavy ions can be used to treat tumors efficiently, as it is currently done in Japan and Germany

Introduction

The biological effectiveness of ionizing radiation strongly depends on the linear energy transfer, or LET, and it is well known that it is, for many endpoints, higher than sparsely ionizing radiation for LET values between 50 and 200 keV/ m in water. This different biological effectiveness os normally attributed to the different spatial distribution of lesion density in the DNA. While physicists know very well, form nuclear emulsions, how different a track of a heavy ion is compared to photons, more recently this could be visualized directly in mammalian cells, exploiting markers of DNA lesions such as phosphorilated histone γH2AX (Fig. 1) [1] or the accumulation of GFP-tagged repair proteins, such as 53BP1 (Fig. 2) [2]. Clearly, heavy ions produce “streaks” of DNA lesions in the cell nucleus, and the density of lesions increase with LET (Fig. 1), and they can be hardly repaired or moved following exposure (Fig. 2). This observation begs the question of whether the damage induced by heavy ions is different from that produced by X-rays. The answer is unfortunately not simple: even if the DNA damage is more difficult to repair, this may lead to an increased cell killing, but not necessarily to increased late risk: a dead cell cannot represent a risk, although the bystander effect may play a dominant role in explaining the effectiveness of high-LET radiation for late effects.

1. Heavy ion radiobiology

Because heavy ions are not present on Earth, their study is not relevant for radiation protection, and neither it has been for radiation therapy for many years. However, heavy ions are now often used in therapy [3] and they represent a major risk for human space exploration [4] (Fig. 3).

1.1. particle therapy

The rationale of oncological particle therapy is simply base don the different energy deposition of charged particles (the Bragg curve) and photons (exponential attenuation). Fig. 4 immediately suggests that charged

particles have a better energy deposition pattern than X-rays for therapy, as recognized by Wilson already in 1946. Protontherapy is today widely spread in the world, and is considered a cutting-edge technology, with clinical results at least comparable to X-ray IMRT. However, apart from the favorable dose distribution, protons do not really add biological advantages, as their RBE is close to 1.

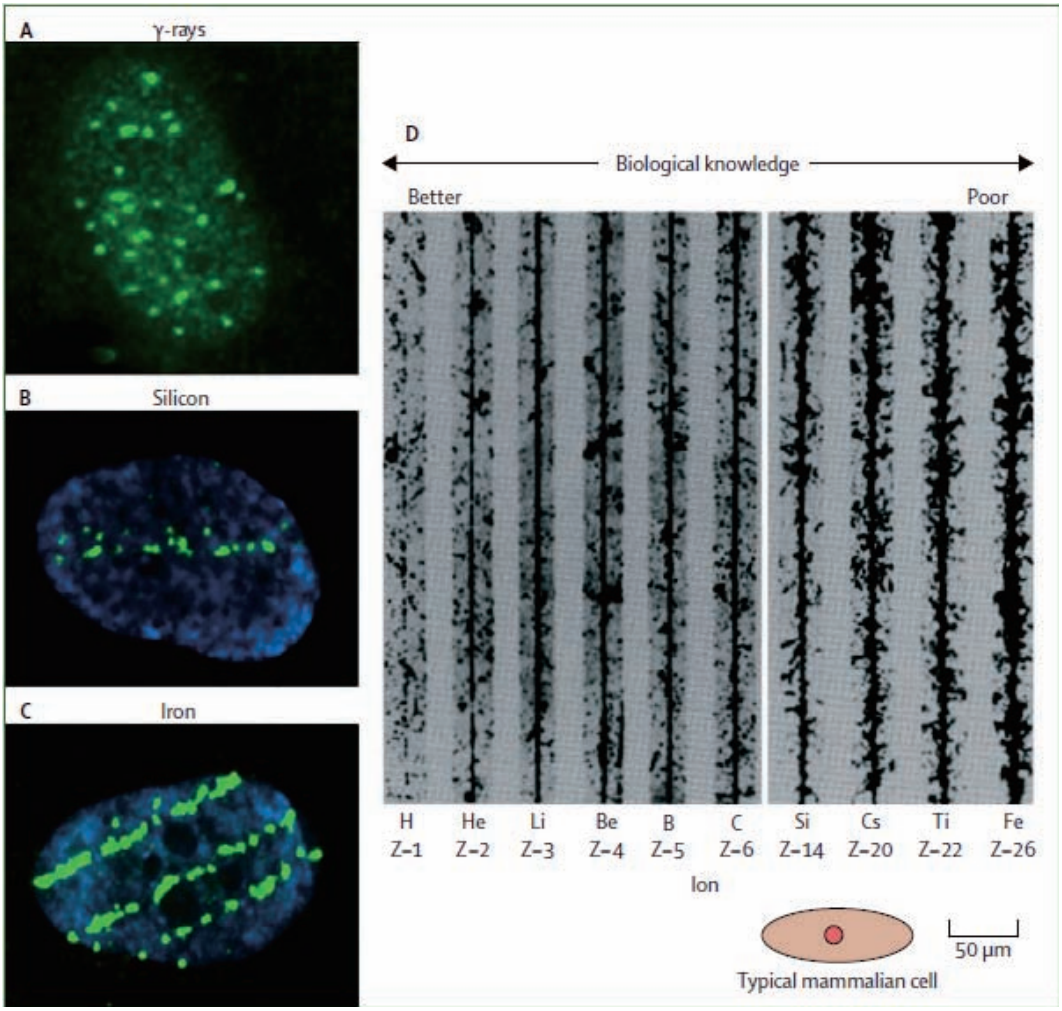


Figure 1 Three nuclei of human fibroblasts exposed to (A) γ-rays, (B) silicon ions, or (C) iron ions; and immunostained for detection of γ -H2AX. Every green focus corresponds to a DNA double-strand break. In the cell exposed to sparsely ionizing γ -rays (A), γ H2AX foci are uniformly distributed in the nucleus. Cells exposed to heavy ions show DNA damage along tracks—one silicon (B) and three iron (C) particles, respectively. Spacing between DNA double strand breaks is reduced at very high-LET. (D) Tracks of different ions, from protons to iron, in nuclear emulsions, show increasing LET as charge, Z, increases. From ref. [1].

On the other hand, heavy ions combine an increased biological effectiveness to a high RBE, and reduced oxygen enhancement ratio (OER), in the Bragg peak. Carbon ions are for instance low-LET (about 10 keV/μm) in the entrance channel, but high-LET (up to 80 keV/μm) in the Bragg peak, thus providing sparing of the normal tissue and high effectiveness in the tumor. The clinical results, so far based on a fairly limited number of cancer patients (about 5000) are indeed very good, and after the clinical trials in NIRS (Japan) and GSI (Germany), several new centers are under constructions in Europe and Asia.

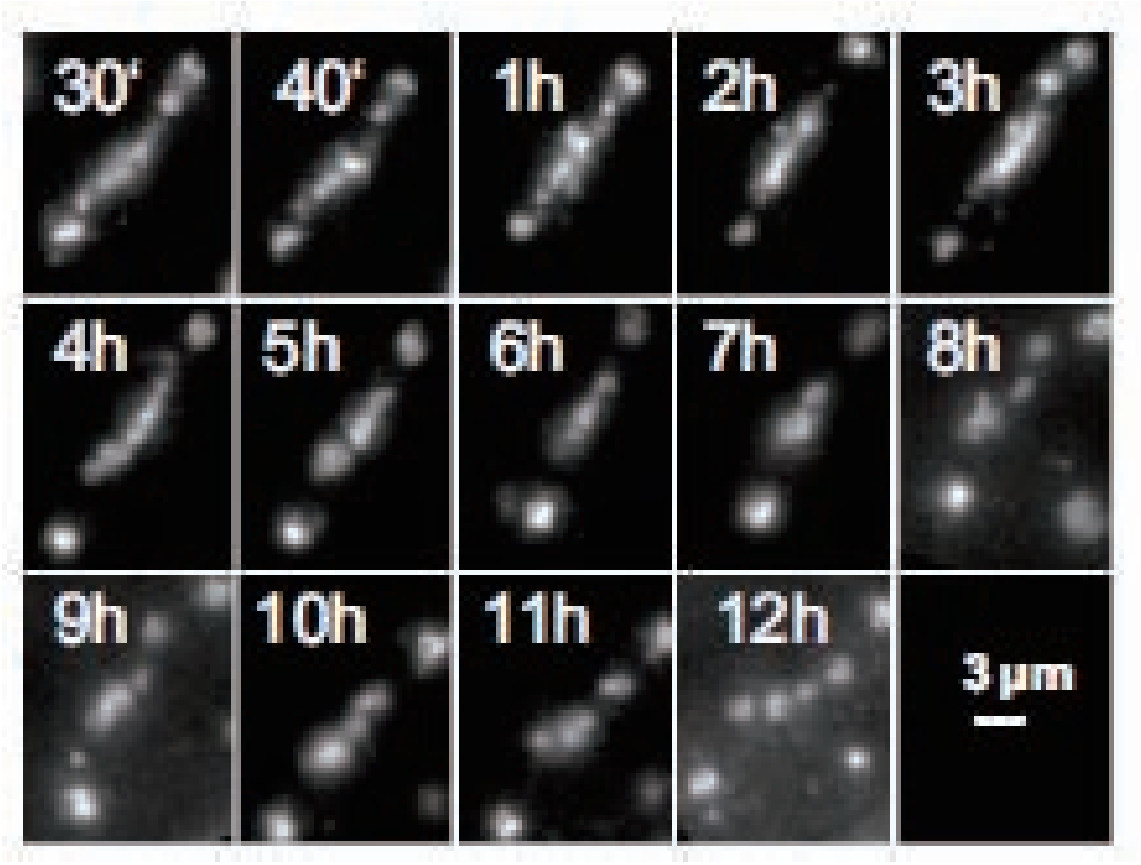
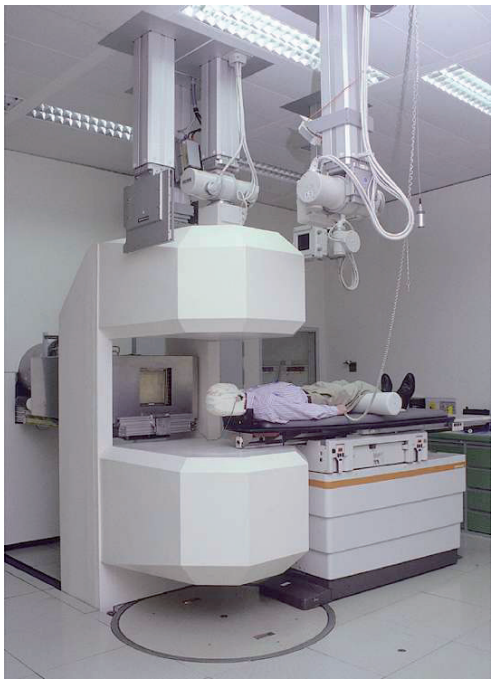


Figure 2 Quantitative analysis of the motion of DNA double-strand breaks (DSBs) after high LET irradiation. Time-dependent changes of a single Ni-ion-induced 53BP1-GFP streak in a human tumor cell showing the typical motional behavior of individual proteins along the trajectory over the time course of 12 h after irradiation. Compared to Fig. 1, these pictures show the evolution of the damage in living cells, exploiting GFP-tagged proteins expressed in the cell, instead of fixing and staining the samples. From ref. [2].

1.2. RADIATION PROTECTION IN SPACE

Although protons are by far the most common particle in space radiation, heavy ions play a major role because energy deposition increase with z^2, and the RBE increases with LET. Therefore, heavy ions are nowadays acknowledged by space agencies as a major barrier to human space exploration. Cancer risk is of course the main concern, because it is well documented that radiation can induce cancer, but the RBE of heavy ions is not known, due to the lack of epidemiological studies and the only limited animal studies, performed at particle accelerators [4]. In addition to cancer, several others late effects cause concern, including damage to the central nervous system, cataracts, risk of cardiovascular diseases, and hereditary effects. Both NASA and ESA support large experimental campaigns to study these effects, considering that space agencies are now shifting their programs to exploration.



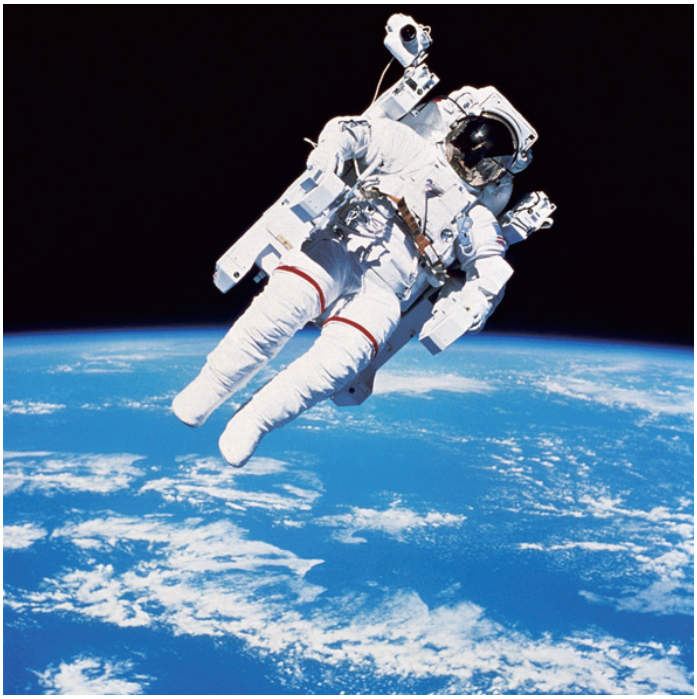


Figure 3 Interest for radiobiology of heavy ions is linked to two main applications: cancer therapy (left) and protection of astronauts in long term space missions (right). In one case, we are interested to exploit the ability of heavy ions to kill cells; in the second, to protect the crews from long-term late effects. Although the exposure conditions are very different (high dose, fractionated, localized irradiation in therapy; low dose, chronic, whole body in space), the two topics share several research topics, such as studies on stochastic risk of heavy ions, or on radioprotectors (Table 1).

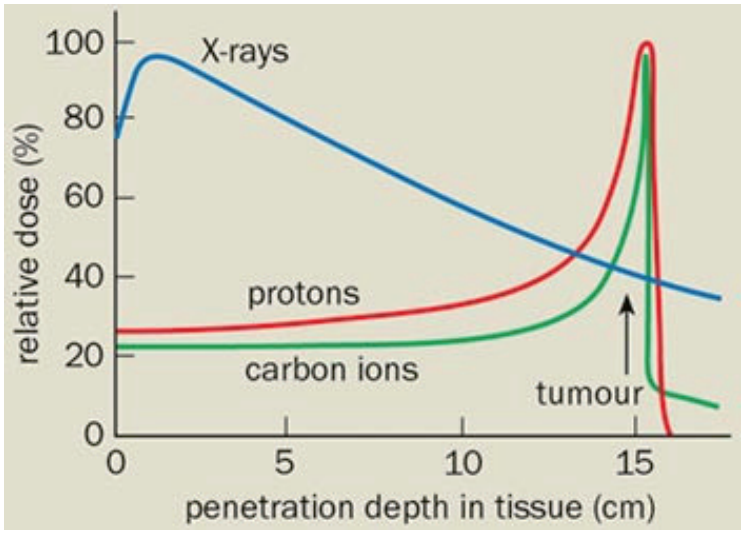


Figure 4 Rationale of using charged particles for cancer therapy. While X-rays deposit more energy on the surface than in the tumor, the opposite holds for charged particles, such as protons and carbon ions.

The NASA program is based at the Brookhaven National Laboratory (Upton, NY), whereas the European program is based at GSI (Darmstadt, Germany).

Notwithstanding the large differences in exposure conditions (high dose, fractionated acute partial-body exposure in therapy; low dose, chronic whole-body exposure in space), the two topics share several research topics as summarized in Table 1.

Table 1 – Some research topics relevant for both hadrontherapy and space radiation protection.

	Hadrontherapy	Space Radiation Protection
Particles	H and C.	All ions from H to Ni.
Maximum energy	~ 400 MeV/n	~ 10 GeV/n
Dose	60-80 Gy-eq. in the target volume. Dose to the normal tissue depend on the treatment plan.	50-150 mSv on the Space Station, up to 1 Sv for the Mars mission
Exposure conditions	Partial-body, fractionation (2 Gy-eq./day in the target volume)	Total-body, low dose-rate (1-2 mSv/day)
Individual radiosensitivity	Patient selection, personalized treatment planning	Personalized medical surveillance of the crewmembers
Mixed radiation fields	Effects of primary particles and fragments for tumor cell killing and side effects	Cosmic radiation is a mixed field. Effects of shielding.
Late stochastic effects of heavy ions	Risk of secondary cancers in patients	Risk of cancer in astronauts
Normal tissue deterministic effects	Early and late morbidity	Cataracts, CNS damage, other late degenerative effects
Radioprotectors	Protection of the normal tissue, but not of the tumor. Drugs.	Protection from heavy ions at low doses and protons at high doses (solar particle event). Dietary supplements
Biomarkers	Predicting risk of secondary cancers or late morbidity	Reducing uncertainties in risk estimates
Bystander effect	Role in tumor cell killing	Role in stochastic risk at very low fluence

2. Conclusions

Biological effects of densely ionizing radiation are becoming a key topic in radiobiology, because of the interest for heavy ions coming from space radiation protection and particle therapy. Large experimental campaigns are currently under way at accelerators, and it is likely that they will lead to a reduction of the uncertainty on the late risk of heavy ions.

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History and Development of Various Particle Therapies

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The primary principle of radiotherapy lies on precise dose localization in the target lesion while minimal damage to the surrounding normal tissues. The success of treatment therefore largely depends on the performance and capacity of the irradiation machine, radiation treatment planning system, and other related devices. This becomes particularly clear, when we notice that the higher energy of photons (x- and gamma-rays), which has reached the order of MV in 1950s, contributed significantly to the improvement in the therapeutic outcome. Historically, high-energy accelerators, such as telecobalt machine and linear accelerators, were developed and applied to practical use in the 1950s, which marked the beginning of modern radiotherapy. In the late 20th century, high-tech radiotherapy approaches involving intensity modulated radiotherapy and three-dimensional stereotactic radiotherapy became popular, contributing to the improvement in applicability and treatment outcomes of radiotherapy.

Charged particle therapy, which possesses favorable dose-localization profiles and larger biological effects as compared to photon therapy, has a history of 50 or more years, similar to the high-precision photon therapies mentioned above. It is one of the key players that remarkably enhanced the possibilities for radiotherapy. Particle beams include a wide variety of particles. Particular concern has been recently focused on charged particles, of which proton and carbon ion beams are front-runners in the world. The major characteristics and a brief history of some of the major particle therapies are presented below.

1. Fast Neutron Radiotherapy

The world-first clinical application of the particle beam was fast neutron radiotherapy that utilized the neutron beam [d(8) + Be], obtained from the 37-inch cyclotron at Berkeley, USA in September 28, 1938. Since then, fast neutron radiotherapy had been performed in various areas in the world. In the late 1970s, this therapy reached its apex in Europe, USA, and Japan, with researchers reporting the effectiveness of this therapy for the treatment of salivary gland tumors, head-and-neck non-squamous cell carcinomas, bone and soft-tissue tumors, malignant melanomas, and other tumors that were not responsive to conventional x-ray radiotherapy. For other tumors, however, this therapy failed to provide favorable control rates and caused unexpectedly severe late reactions, which led an increasing number of research institutions to abandon this method. At present, there are only a few medical centers worldwide performing fast neutron radiotherapy.

2. Pi-Meson Radiotherapy

In 1935 Dr. Yukawa theoretically predicted the existence of mesons, and hat protons and neutrons in the nucleus attract one another by exchanging pi mesons. The pi mesons once found their way into clinical

application for cancer radiotherapy in the past; negative pi mesons were used for clinical treatment. These elemental particles are generated by collision of 400-MeV or higher protons (or electrons) with nucleons in the target. When negative pi mesons are employed in radiotherapy, they are captured by the medium nucleus at the end of flight path, releasing short-range ions (star production), which are a mixture of high- to low-LET components. Pi-meson radiotherapy was welcomed with great enthusiasm, and there were three institutions that conducted this therapy in 1980s. However, all of them eventually discontinued the treatment; the last institution closed the therapy in 1994. The major reasons for the discontinuation were that, against the initial expectations, the pi meson had a relatively low RBE value of 1.5, unsatisfactory dose distribution profile, and poor clinical outcome.

3. Proton and Carbon Ion Radiotherapy

At present, proton and carbon ion radiotherapy is one of the most attractive cancer therapy. The team of researchers led by J. Lawrence and C. Tobias at Berkeley Lab, USA pioneered the medical application of protons beams from 1954 to 1957. Since then proton therapy has become popular in the world. Analysis of clinical data showed that proton beam therapy was effective for the treatment of malignancies including skull base tumors, malignant choroidal melanomas, liver cancers, prostate cancers, and pediatric cancers. These diseases are known to affect a large population of patients. Of these, malignant choroidal melanomas had the largest number of patients treated with proton beam therapy. This type of tumor was the first that was treated safely with a large dose of 60–70 GyE in 4 to 5 fractionations (in one week).

The Berkeley research teams then embarked on helium ion radiation therapy in 1957 and neon ion radiotherapy in 1975. Unfortunately, the Berkeley Lab terminated all radiotherapy programs in 1992. As if the baton was passed across the Pacific, the National Institute of Radiological Sciences, Japan installed the world's first heavy charged particle accelerator designed for medical use (HIMAC) in 1993. The Institute started carbon ion radiotherapy in June the following year. The Institute succeeded to obtain an approval in 2003 by the Ministry of Health, Labour and Welfare for performing carbon ion therapy under the title of 'Heavy Charged Particle Therapy for Solid Tumor' as part of the Government-sponsored Highly Advanced Medical Technology program. Carbon ion radiotherapy so far has been applied to more than 5,400 patients at NIRS, and its effectiveness for the treatment of various types of malignant tumors has been established. It has been demonstrated that the oxygen level in the tumor lesion or the cell cycle-dependent radiosensitivity does not significantly influence the biological effects of heavy charged particle beams. This therapy could therefore be effective for the treatment of many types of radioresistant tumors, such as bone and soft-tissue tumor, skull base tumor, head-and-neck tumor, lung cancer, liver cancer, prostate cancer (high-grade), and recurrent rectal cancer. It is characterized by the short treatment period for most types of tumor.

In addition to the NIRS, Japan, there are four other facilities that are performing heavy charged particle therapy in the world: Heidelberg Ion Therapy Center, Germany; Hyogo Ion Beam Medical Center, Hyogo, Japan; Gunma University, Gunma, Japan; and the Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou, China. A new facility will be opened in 2011 at the National Center of Oncological Hadrontherapy (CNAO), Italy. Furthermore, two other sites in Germany and one in China are currently under construction.

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Carbon Ion Radiotherapy for Patients with Bone and Soft-tissue Tumors

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Malignant tumors that originate in the bone and soft tissues (e.g., muscle and adipose tissue) are termed sarcomas, which differ from carcinomas (e.g., lung cancer and stomach cancer). Sarcomas have a much lower incidence than other cancers. In Japan, approximately 500 and 2000 patients are diagnosed every year with malignant tumors of the bone and soft tissue, respectively. Unlike other cancers, sarcomas are not lifestyle-related, and occur at a considerably higherrate among younger subjects. Sarcomas involve a wide variety of histological types (e.g., osteosarcoma, chondrosarcoma, liposarcoma) and may develop in any part of the body. Depending on the combination of the histological type and the site of development, therapeutic approaches may vary, and the same treatment may result in different outcomes for different tissues.

Multidisciplinary approaches including surgery, chemotherapy (anti-cancer drugs), and radiotherapy have been most successful for the treatment of bone and soft-tissue tumors in the last 30 years. In particular, the survival rate has greatly improved for patients with osteosarcomas of the extremity due to the progress in chemotherapy. In addition, dramatic advancement in surgical techniques and prosthetic technology has markedly improved the limb salvage rate.

The first-line treatment for bone and soft-tissue tumors is almost always surgery. Not all cases, however, are resectable, and the operability of a tumor depends on its site, size, and depth of invasion. Tumors of the extremities are often completely curable, whereas tumors involving the spine, pelvis, or other axial part of the body may not allow resection at all in advanced cases. Some patients undergoing surgical resection may run the risk of being deprived of excretory function or of suffering a major loss of ambulatory function. Unresectable tumors are generally treated with external radiation therapy or brachytherapy combined with chemotherapy. However, chemotherapy is not always effective for the treatment of sarcomas, and conventional radiotherapy achieved good results for only a few types of sarcomas. Thus, unresectable sarcomas had a very poor prognosis.

Heavy charged particles (e.g., carbon ion) have a higher biological effectiveness and more favorable dose distribution profiles than ordinary radiation beams (x-rays or γ-rays). The use of these particles provides the target tumor site with a large amount of tightly-focused irradiation possessing a high tumoricidal effect. An additional advantage of the carbon ion radiotherapy is that it causes minimal patient discomfort or pain.

The standard protocol for the treatment of bone and soft-tissue tumors with the carbon ion radiotherapy consists of 12 to 16 irradiation sessions delivered over three to four weeks, once daily four times per week. The patient will lie in either a supine or prone position on the table for 20 to 30 minutes. The irradiation with carbon ion beams lasts for a few minutes. The patient feels no pain or heat, so he or she can barely notice when irradiation is taking place. Ordinary treatment programs are run in an inpatient setting. However, patients may request an occasional overnight stay outside the hospital. They can be discharged on the day when the treatment terminates.

We started a clinical trial in June of 1996 to evaluate the safety and efficacy of carbon ion radiotherapy for the treatment of unresectable bone and soft-tissue sarcomas. The Ministry of Health, Labour and Welfare approved the treatment method under the Advanced Medical Technology program in October of 2003. A total of 764 patients with bone and soft-tissue sarcomas were treated at our hospital from 1996 until February 2010. In fiscal year 2009, 140 patients were treated.

Among the bone and soft-tissue sarcomas treated with carbon ion radiotherapy at our hospital, sacral chordomas accounted for the largest proportion. Sacral chordoma is a rare tumor, occurring in 20 to 30 patients among the entire Japanese population each year. We treated 22 patients in fiscal year 2009, which comprised a large majority of the Japanese sacral chordoma patient population. Surgery is the first-choice treatment for these patients, although it is not always possible. Since sacral chordomas develop gradually, they are often undetected until they start to cause chronic pain or other symptoms. Many patients present with a huge sacral chordoma mass. The sacrum houses a group of nerve fibers that innervate the lower body and excretory functions. Excision of these nerves along with the tumor mass may cause permanent gait, excretory, and other disabilities, significantly impairing the patients' quality of life. Sacral chordomas frequently occur among the elderly population. Because sacrectomy will place an excessive physical burden on elderly patients, they are often recommended for carbon ion radiotherapy According to the latest data on the treatment outcomes on carbon ion radiotherapy for sacral chordomas, the 5-year local control rate was around 80%, which was comparable to that of surgery. Regarding the post-treatment salvage rates in 30 patients who were followed up for 5 or more years, no patient had undergone a colostomy due to an adverse reaction from the carbon ion radiotherapy as of the time of the last observation. Ninety percent of the patients retained the ability to walk on their own, and 50% did not require a cane, stick, or other walking aid. The excellent outcomes of the treatment of sacral chordomas at our hospital were published in *Clinical Cancer Research* in 2004 and the *Year Book of Oncology* in 2006. To date, more than 100 patients with sacral chordomas have been treated at our facility, probably a world record for the largest number of cases of sacral chordomas treated by a single institution.

Osteosaromas and chondrosarcomas of the trunk constitute the next largest group of patients. A large majority of patients with these tumors are not indicated for surgery, because of the tumor site or size, old age, and concurrent chronic illness. For the

treatment of osteosarcomas of the extremity, which develop at a higher incidence among young patients, a paradigm based on the combination of surgery and chemotherapy has been well-established, and carbon ion radiotherapy is unlikely to provide additional advantages over this established treatment regimen. Owing to the advances in limb salvage techniques, most cases will not experience post-surgical problems in their daily function.

Nearly 15 years have passed since the first use of the carbon ion radiotherapy for bone and soft-tissue tumors at our hospital. As mentioned above, the numbers of patients with these tumors treated at our hospital have been rising steadily each year. In particular, the last five years have witnessed a rapid increase, which reflects the growing popularity and recognition of the technique, as well as the potential needs among not only health-care providers, but also patients. In order to meet the expanding medical demands, we will need to accumulate more evidence to broaden the indications for this novel technique. Carbon ion radiotherapy could be an alternative to surgery that can be applied to patients with unresectable tumors, elderly patients with impaired health status, and those who are anticipated to experience permanent surgery-induced physical disabilities.

Carbon Ion Radiotherapy for Lung Cancer

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Abstract

Although stage I non-small cell lung cancer can often be cured by surgical resection, in some cases, surgery cannot be performed or is refused by the patient. There is a critical need to develop safe and effective treatments to reduce the mortality of lung cancer in such patients.

Carbon ion radiotherapy for lung cancer was first performed in November of 2009, and 918 patients have been treated as of December 2010. For peripheral type stage I lung cancer, the treatment period was gradually shortened from 6 weeks (18 fractions) to 3 weeks (9 fractions) to 1 week (4 fractions) to determine the safety and efficacy of the treatment. A clinical trial examining the treatment of patients in a single day is just ending

In the phase II clinical trial, the adverse effect on normal tissue was 91.8% in a five years local control rate, not showing a pulmonary response grade of 3 or more, which indicates clinically problematic cases.

It appears that carbon ion radiotherapy contributes to the reduction of lung cancer mortality, and may represent a valid alternative local therapy for inoperable cases.

Introduction

Due to the increase in lung cancer screening, stage I lung cancers are being diagnosed more frequently than in the past. Although most of these cases are thought to be radically curable by surgery, there are still some inoperative cases, including patients with pulmonary complications or cardiac disease, or patient who refuse surgery. It is therefore necessary to develop safe and effective treatments to reduce the lung cancer mortality for such patients.

We herein report the results of a clinical trial of carbon ion radiotherapy for peripheral type stage I non-small cell lung cancer.

Carbon ion radiotherapy was first used for lung cancer in November of 2009, and a total of 918 patients have been treated using the technique as of December 2010. For the initial treatment, a dose escalation study of 18 fractions over 6 weeks was performed for peripheral type stage I lung cancer, central type lung cancer, pulmonary hilum proximity peripheral type lung cancer, and lung cancer that had invaded the chest wall (as preoperative irradiation) [1-3]. In the preoperative irradiation of the chest wall cancer, a strong anti-tumor effect was confirmed in the pathological findings after the lung was removed surgically[4]. For peripheral type stage I non-small-cell lung cancer, the clinical trial proceeded, with a reduction in the fractions from 9 fractions (3 weeks) [5] to 4 fractions (1 week) [6].

At present, a once a week dose enhancement evaluation for the peripheral type stage I non-small-cell lung cancer is underway (Figure). Even though the exposure period is shortened, no complications have occurred in the skin or the lungs. Similar results have been seen using 9 fractions or 4 fractions.

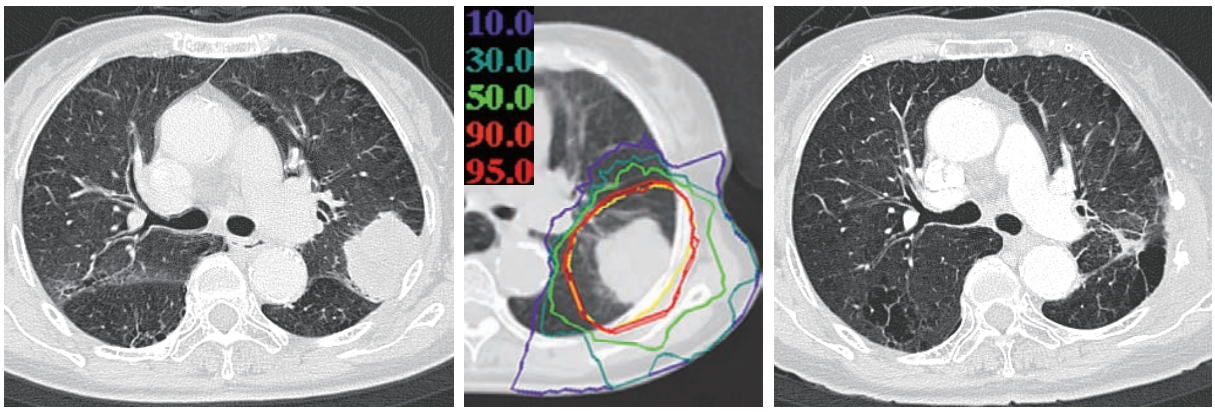

Figure: Clinical course of 71-year-old female (T2N0M0 squamous cell carcinoma) after CIRT (40GyE/ single fractionation). CT (A), dose distribution map (B), and CT (C) at 18 months after CIRT are shown. Apparent tumor shrinkage was observed without severe lung fibrosis.

The results of carbon ion radiotherapy for peripheral type stage I non-small-cell lung cancer

Objective and methods

Because at least 5 years has passed since all of the patients who received 9 fractions and 4 fractions, we report the extended clinical course of those cases.

There were a total of 131 cases, including 94 males and 37 females, with an average age of 74.5 years of age. Out of the 131 focii, there were 72 T1 tumors, which are ≤3cm in diameter, and 59 T2 tumors, which were >3 cm in diameter.

With regard to the histological type, there were 85 adenocarcinomas, 43 epidermoid cancers and 3 other types. Out of the 131 cases, 51 cases were treated with 72.0GyE/9 fractions and 80 cases were treated with 52.8GyE for stage IA and 60.0GyE for stage IB in 4 fractions.

When asked for the reason(s) why they opted to participate in our carbon ion radiotherapy, trial, 76% of the cases had entered the trial because they were contraindicated for surgery, and a few patients had refused surgery. Low pulmonary function accounted for approximately 60% of the cases that were considered inoperable.

Results

Indicating the safety of the technique, no pulmonary reaction of grade 3 or higher was found, nor were there any other clinically important signs of any effect on normal tissues[5,6]. In an analysis targeting 28 patients who were ≥80-years-old, the impairment of lung function was also mild[7].

With regard to the anti-tumor effect, the local control rate was 93.0% at 3 years, and 91.8% at 5 years. Taking into account each tumor size, the local control rates at 3 years/5 years were 98.6%/96.7% in T1 patients and 85.0%/85.0% in T2 patients. Moreover, even patients with T2 tumors (>3cm in size) showed good local control. The cumulative 3 year crude survival rate was T1:79.9% and T2:47.5%, and the cumulative 5 year crude survival rate was T1:50.7% and T2:32.2%. The cause-specific survival rates at 3 years and 5 years were 89.9%/82.7% in patients with T1 and 65.4%/55.2% in those with T2 tumors.

Comparison with other therapeutic methods

1）Comparison with stereotactic body radiotherapy and proton beam radiotherapy

In existing radiotherapy against inoperative early lung cancer cases, the local control rate was approximately 30-70% at 3 years. However, good results for lung cancer therapy have recently been

reported for stereotactic body radiotherapy when the radiation (stereotactic irradiation) was applied using X-rays[8,9]. The comparison of various techniques[10-12] including proton beam radiotherapy, is shown in Table 1. Carbon ion radiotherapy has better local control against T2 tumors compared with the other therapeutic methods.

Table 1: Local control in stage I lung cancer after carbon ion RT, stereotactic body RT and proton beam RT

Author		Therapy	Case(IA/IB)	Local control (IA/IB)
Baumann 8)	2009	SBRT	57(40/17)	3yr 92%
Onishi 9)	2007	SBRT	87(63/24)	5yr 86.6%
Bush 10)	2004	Proton	68(29/39)	3yr 74% (87%/49%)
Nihei 11)	2008	Proton	37(17/20)	2yr 80% (94%/62%)
Iwata 12)	2010	Proton	57(27/30)	3yr 81%
Miyamoto 5)	2007	Carbon	50(29/21)	5yr 94.7%
Miyamoto 6)	2007	Carbon	79(42/37)	5yr 90% (98%/80%)

2) Comparison with surgical treatment

Table 2 compares the results of 5-10 years of experience with carbon ion radiotherapy with the surgical results obtained during the same time. According to the results of lung cancer resection cases in the year of 1999 joint survey by the Japan Lung Cancer Society and the Japanese Respiratory Surgery Society[13], the cumulative 3 year crude survival rate was 84.4% for patients with clinical stage IA and 70.3% in patients with IB tumors, while the cumulative 5 year crude survival rate was 77.0% for those with IA and 60.1% for those with IB disease. For carbon radiotherapy, the IA 3 year crude survival rate was 79.9%, however, the cause-specific survival rate was 89.9%. The reason why the crude survival rate was inferior to the surgery rate was likely because the mean age of the inoperable cases was 10 years higher than the surgically-treated cases. Therefore, there were many deaths caused by other factors.

Table 2: Comparison between carbon-ion RT and surgery

	c-Stage	Overall survival (cause specific) %	
		3yr	5yr
Carbon-ion Radiotherapy (NIRS)	IA	79.9 (89.9)	50.7 (82.7)
	IB	47.5 (65.4)	32.2 (55.6)
Surgery*	IA	84.4	77.0
	IB	70.3	60.1

* Cited from 13) in the Reference

On the other hand, the 5-year cause-specific survival rate for carbon beam therapy for IB patients was 55.6%. The reasons for this difference are the rate of occurrence of metastasis or recurrence, which were as high as 63% in patients with IB tumors compared with IA, which was only 24%. To improve the prognosis of stage IB patients, it will be necessary to consider adjuvant chemotherapy or other therapy.

The carbon beam therapy irradiated the area that corresponded to the partial excision. Considering the results of limited surgery, including a partial excision and segmental resection, the 5-year crude survival rate is approximately 50% for clinical stage I patients. As many as 76% of our patients were medically inoperable, and had no real treatment options. Carbon beam therapy can therefore be considered a less-invasive and more easily tolerated alternative for inoperable patients or those who refuse surgery.

Conclusion

It appears that carbon beam therapy will therefore positively contribute to the reduction of lung mortality, and it is a safe and effective local therapy method that represents a valid alternative for inoperative lung cancer patients.

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Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer

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1. Characteristics of Locally Recurrent Rectal Cancer

The large intestine starts at the ascending colon, which is connected to the small bowel, and ends at the rectum, which extends from the sacral promontory to the anal canal. In 2008, approximately 43,000 patients died of colorectal cancer in Japan which is the third most common cause of cancer deaths, after lung and stomach cancers. Approximately 100,000 patients were diagnosed with colorectal cancer in 2004, thus making it the second most common type of cancer after stomach cancer. The analysis of the post-operative recurrence rates of colorectal cancer indicates a higher rate for rectal cancer than colon cancer. When compared by the site of recurrence, rectal cancer had a more than three times higher local recurrence rate than colon cancer.

With the recent advances in surgical techniques and procedures, the pelvic recurrence rate of rectal cancer has been decreasing, however the post-operative recurrence rate is still 5% to 20% today. Surgical resection is the first choice for locally recurrent rectal cancer, although total pelvic extenteration or another highly invasive procedure is often required. In many cases, locally recurrent rectal cancers are not completely resectable so generally surgical resections are not selected. The comparison of resection rates by the type of tumors shows that the resection rates were in the range of 40% to 50% for liver metastases and 20% to 40% for lung metastases, whereas the rate was 10% to 40% for locally recurrent colorectal cancers (Table 1)[1,2] Curative resection of these tumors will lead to a survival rate similar to those for other types of recurrences and metastases.

Table 1. Resection and Survival Rates by Site of Recurrence

	Resection rate	5-Year survival rate
Local Recurrence	10-40%	20-40%
Liver metastasis	40-50%	35-55%
Lung metastasis	20-40%	40-50%

Radiation therapy is often indicated for unresectable cases of locally recurrent rectal cancer; most of the past studies on conventional x-ray radiotherapy reported a 12-month median survival and a 10% 3-year overall survival. The use of adjuvant chemotherapy elevated the local control rate up to around 20%, which is far from satisfactory. Heavy charged particle beams have been shown to exert potent

anti-tumor effects against radioresistant adenocarcinomas. To improve both the long-term local control and survival of locally recurrent rectal cancer, we have initiated a radiation dose-escalation trial using heavy charged particles.

2. Summary of the Phase I/II and Phase II Studies of Post-Operative Carbon Ion Radiotherapy for Recurrent Rectal Cancer

A phase I/II study of post-operative carbon ion radiotherapy for the treatment of recurrent rectal cancer was started in April 2001. The purpose of the study was to evaluate the tolerance for and effectiveness of heavy charged particle radiotherapy in patients with locally recurrent rectal cancer. In order to determine the appropriate radiation dose, this study adopted a dose-escalation design. This study was continued until February 2004, and enrolled 38 patients for treatment. Subsequent to this study, a phase II study was initiated in April 2004, as part of the government-sponsored Highly Advanced Medical Technology program. In this study, the total radiation dose was fixed at 73.6GyE. This study is ongoing as of the time of writing.

3. Study Treatment

The patient inclusion criteria for this study included (1) post-operative recurrence of a tumor limited to the pelvis (including its surrounding soft tissue) after curative resection of rectal cancer, and (2) at least a 5-mm gap between the recurrent lesion and radiosensitive organs, including the gastrointestinal tract and bladder. Exclusion criteria were (1) a history of radiation therapy on the planned target site of the carbon ion radiotherapy and (2) the presence of multiple primary tumors. Patients were first treated with a total dose of 67.2 gray equivalent (GyE) in 16 fractions over 4 weeks. The total dose was increased by 5% in a stepwise manner to 70.4 and 73.6 GyE, depending on the tumor response and adverse effects. The phase II study employed a total dose of 73.6 GyE, which was the highest total dose attained in the preceding study. A preliminary analysis was conducted on 140 patients (148 lesions) who completed the treatment by the end of February 2010.

4. Treatment Outcomes

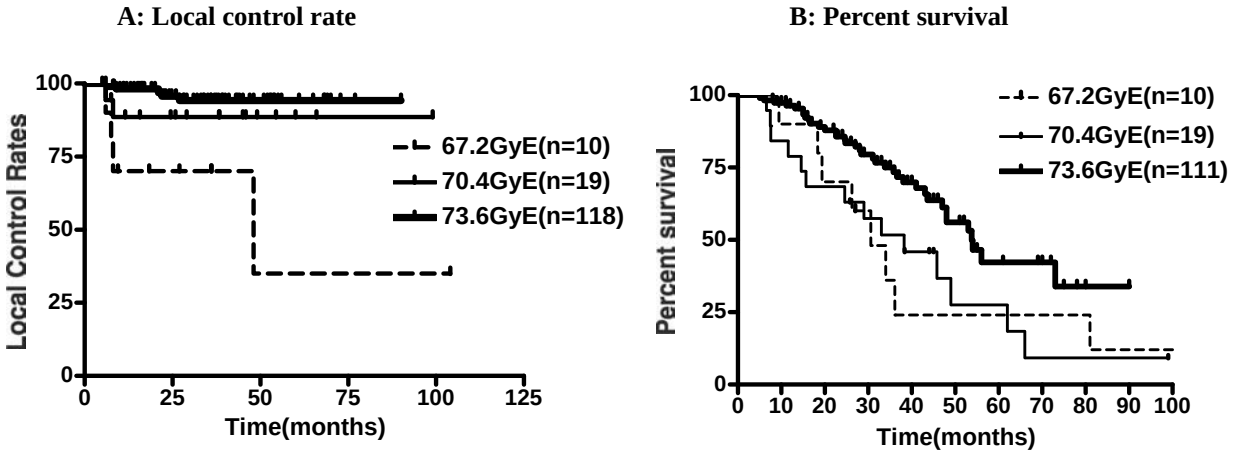
(A) Normal-tissue Reactions

No acute grade 3 or higher adverse reactions have been found to date for the gastrointestinal tract and the urinary system. Late adverse events (defined as those occurring no earlier than 3 months after the start of therapy) were observed in 4 patients, who developed a pelvic abscess after tumor necrosis. The tumor was well controlled in all patients.

(B) Tumor response and Survival Rate

The 3- and 5-year local control rates were 88.5% and 88.5% for patients treated with 70.4 GyE, and 95.2% and 95.2% for those treated with 73.6 GyE. These results showed that radiation doses above 70 GyE achieved excellent outcomes (Figure 1A). The 3- and 5-year survival rates were 36.0% and 24.0% for patients treated with 67.2 GyE, 51.7% and 27.5% for patients treated with 70.4 GyE, and 73.5% and 42.3% for those treated with 73.6 GyE. The survival rates showed an increasing trend with the radiation dose (Figure 1B). A significant proportion of study patients reported rapid pain relief.

Figure 1. Results of Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer



(C) Comparison with Other Studies

The results of the patients treated with 73.6 GyE carbon ion radiotherapy were compared with those of other studies in which patients with locally recurrent rectal cancer were treated with other radiation therapies.[3-6] The results are summarized in Table 2. Compared with the conventional radiation therapies yielding local control rates below 30% and 5-year survival rates below 10%, the carbon ion radiotherapy produced excellent results. Next, our results were compared with the surgical results reported from other institutions (Table 3).[7-9] Our results were comparable to or higher than the published surgical results. In light of the fact that most of our cases involved unresectable tumors, our treatment yielded dramatically improved outcomes. In addition, the carbon ion radiotherapy provided a high quality of life for patients during and after treatment, because patients were spared from undergoing artificial sphincter insertion surgery, and were treated in the out-patient setting.

Table 2. Results of Radiation Therapy for Patients with Locally Recurrent Rectal Cancer

Author	(year)	No. of patients	Radiation dose(Gy)	2-y survival	5-y survival	Local control rate
Ciatto S	1982	108	35-50Gy	5% (3y)	3%	-
O'Connell	1982	17	50	45%	0%	24% (2y)
Wong CS	1991	22	45-50	27%	16%	9% (5y)
Lybeert MLM	1992	76	6-66	61% (1y)	3%	28% (3y)
Knol HP	1995	50	60	27%	8%	-
Murata	1997	18	12-60	44% (1y)	-	46%
NIRS	**2010**	**111**	**73.6**	**86%**	**42%**	**95% (5y)**

Table 3. Results of Surgical Therapy for Patients with Locally Recurrent Rectal Cancer

Author	(year)	No. of patients	1-y survival	2-y survival	5-y survival
Kato	1994	32	93%	82%	46%
Garcia-Aguilar J	1999	42	88%	62%	35%
Wanebo	1999	53	91%	62%	31%
Salo JC	1999	71	88%	75%	31%
Saito N	2003	43	91%	78%	39%
Moriya	2004	48	95%	76%	36%
NIRS	**2010**	**111**	**97%**	**86%**	**42%**

5. Widening the Applicability of Carbon Ion Radiotherapy

Pelvic recurrent tumors are often located in close proximity to the digestive tract. Consequently, a significant proportion of patients were often judged as ineligible for carbon ion radiotherapy, because the digestive tract could not be excluded from the irradiation field. At our hospital, therefore, we adopted a surgical preparatory procedure, to place a spacer between the target tumor and the digestive tract before conducting carbon ion radiotherapy, when the tumor was located close to a sensitive organ. This preparatory procedure has been shown to improve the outcome. We are also currently treating patients with para-aortic lymph node recurrence with 12 fractionated-dose radiation over three weeks, with highly positive outcomes.

6. Conclusion

Carbon ion radiotherapy produced results comparable to the surgical outcomes for patients with locally recurrent rectal cancer. In addition, this minimally invasive therapy ensured a high quality of life for the treated patients.

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Prostate Cancer

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Abstract

Therapeutic outcome of short-term carbon ion radiotherapy towards localized prostate cancer was investigated. We analyzed the biochemical relapse-free rate of 903 cases which were observed for 6 months and more after therapy at the time of February 2010, also we analyzed survival rate, and the incidence of toxicity. 5-year biochemical relapse-free rate of whole cases was 90.9%. The Gleason score, PSA value and clinical stage were the significant predictive factor of relapse-free rate. The difference of relapse-free rate by method of fractionation (20 fractions and 16 fractions) was not found. None but one out of 818 cases who were followed up at least 1 year developed grade 3 lower urological impairment, and incidences of grade 2 were 5.6% in lower urinary tract and 2.0% in the rectum, respectively. Furthermore, in the 16 fractions, the toxicity incidence was lower than 20 fractions. Accordingly, hypofractionation made it possible to reduce the toxicity incidence without reducing the relapse-free rate.

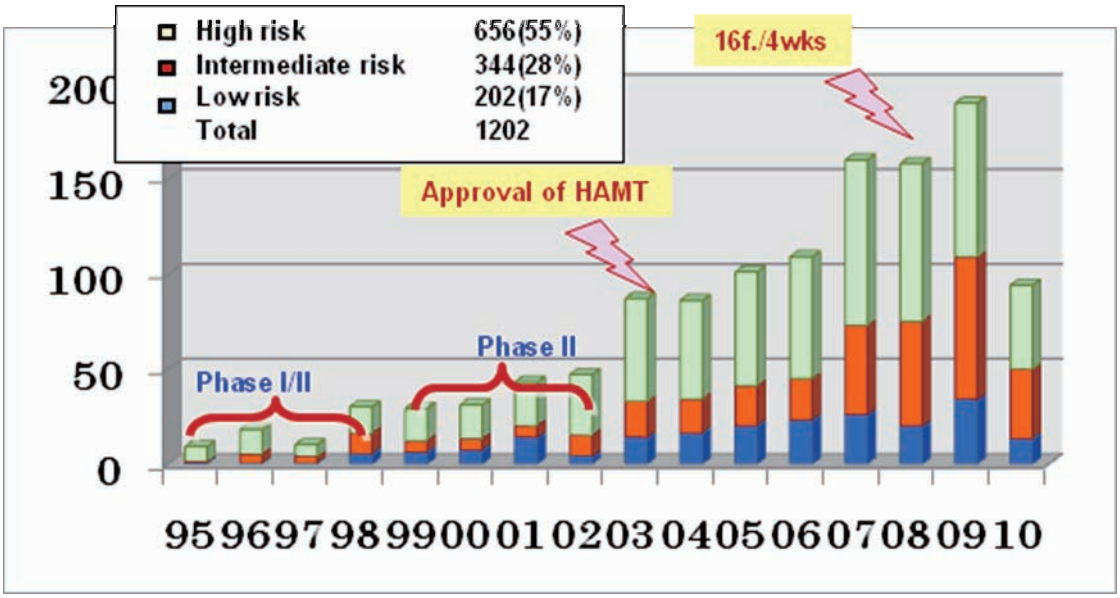
1. Introduction

As for the prostate cancer, recent irradiation therapy including brachytherapy, proton therapy and intensity modulated radiation therapy play active roles, and improving dose distribution and attendant dose escalation is showed to be connected to the outcome improvement. NIRS has been challenging the prostate cancer treatment from June 1995 taking the advantage of the quality of carbon ion beam which has distinguished dose convergence and high anticancer efficacy. First, we performed 3 clinical trials and could establish a therapeutic method which has high quality in both technical and therapeutic strategies. Due to the outcome, we could obtain the government approval of highly advanced medical technology and thereafter we performed more hypofractionation aiming at reducing toxicities and improvement of efficiency, and we proved fruitful.

2. Objective and treatment method

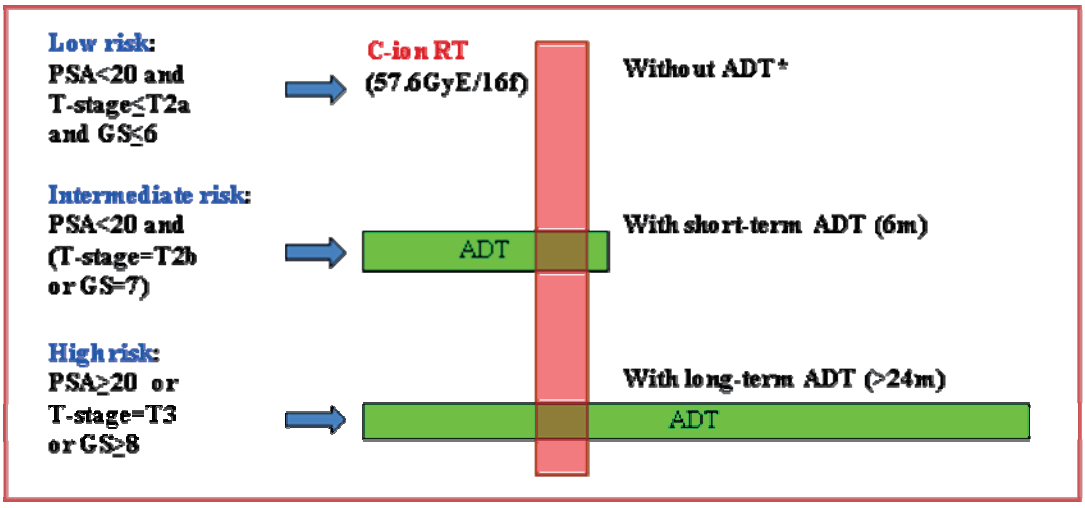
We performed carbon ion radiotherapy against 1202 cases of prostate cancer from the start of clinical trial to July 2010. We treated 96 cases in the early dose escalation trials, 175 cases in the phase II clinical trial, thereafter 909 cases were treated in the approved highly advanced medical technology and 22 cases are in ongoing new clinical trial. The annual cases are gradually increasing, especially greatly increased in 2003 when we gained the approval of highly advanced medical technology and in 2007 when we shortened the therapy term from 20 times in 5 weeks to 16 times in 4 weeks (Figure 1).

Figure 1 Transition by fiscal year of the number of prostate cancer carbon ion radiotherapy cases (Risk group total)



The eligible patient had no metastases and pathological diagnosis was confirmed as prostate cancer case. In the current approach to therapy, the cases are classified into 3 groups (high risk, intermediate risk and low risk) according to the clinical stage, initial PSA value, and pathological Gleason score. For the high risk and intermediate risk groups, we combine long-term and short-term endocrine therapy, respectively (Figure 2). Among actual treated cases, high risk group account for more than a half of the whole cases.

Figure 2 Current treatment policy for each group in NIRS



*ADT; Androgen Deprivation Therapy

As for the carbon ion radiotherapy, first we performed 20 fractions in 5 weeks and after establishing the appropriate dose of radiation and transferred to the highly advanced medical technology, we started 16 fractions in 4 weeks up to today. 562 out of 1202 cases are 20 fractions and 618 are 16 fractions. In a

portion of cases, we started clinical trial of 12 fractions in 3 weeks, and have performed therapy for 22 cases.

The analysis objects were treated by 20 fractions or 16 fractions after the phase II clinical trial and observed for 6 months and more.

3. Results

3-1) Toxicity

Regarding toxicity of carbon ion therapy, we added up the 818 cases which were observed 12 months and more. The result of comparison of late toxicity incidence on various radiotherapies and carbon ion radiotherapy is shown in Table 1. Compared with other various radiotherapies, carbon ion radiotherapy exhibited lower rate toxicity incidence rate, especially, the significant low rate of rectal toxicity. As for the toxicity incidence rate of lower urinary tract system, the carbon ion radiotherapy of 63.0GyE/20 fractions, intensity modulated radiation therapy and proton were approximately the same, however, as for the 57.6GyE/16 fractions, lowering of the incidence rate was gained. As for the toxicity of the rectum, even in 63.0GyE it showed lower rate than X-ray or proton. 57.6GyE showed further lowering of the rate.

Table 1. The Incidence of Late Radiation Toxicity Induced by Various Radiotherapy of the Prostate

Institutes	Radiotherapy	Dose(Gy/f)	No. of pts.	Morbidity ≥ G2	
				Rectum	GU
Christie H.[1]	IMRT	60/20	60	9.5%	4.0%
Princess Margaret H.[2]	IMRT	60/20	92	6.3%	10.0%
Cleveland CF.[3]	IMRT	70/28	770	4.4%	5.2%
Stanford U.[4]	SRT	36.25/5	41	15.0%	29.0%
RTOG9406[5]	3DCRT	68.4-79.2/38-41	275	7-16%	18-29%
	3DCRT	78.0/39	118	25-26%	23-28%
Loma Linda U.[6]	Proton	75.0/39	901	3.5%	5.4%
NIRS	Carbon	63.0/20	216	1.9%	4.6%
	Carbon	57.6/16	274	0.7%	2.6%

1) JH Coote et al. IJROBP 74, 2009 2) JM Martinez et al. IJROBP 69, 2007
3) PA Kupelian et al. IJROBP 68, 2007 4) CR King et al. IJROBP 73, 2009
5) JM Michalski et al. IJROBP 76, 20106) RW Schulte et al. Strahlenther Oncol 176, 2000

3-2) Relapse-free rate and survival rate

Overall survival rate after carbon ion radiotherapy, cause-specific survival rate (survival rate limited to the prostatic cancer caused death), and relapse-free rate are shown in Figure 3. Considering that more than 50 % of the cases are high risk group, the results, such as 5-year overall survival rate of approximately 95%, relapse-free rate of more than 90% can be considered quite satisfactory. Incidentally, there is no difference in the relapse-free rate and survival rate between 20 fractions in 5 weeks and 16 fractions in 4 weeks. Shortening the treatment term did not show lowering of the curative effect.

Figure 3 Survival rate and relapse-free rate of prostate cancer carbon ion radiotherapy cases.

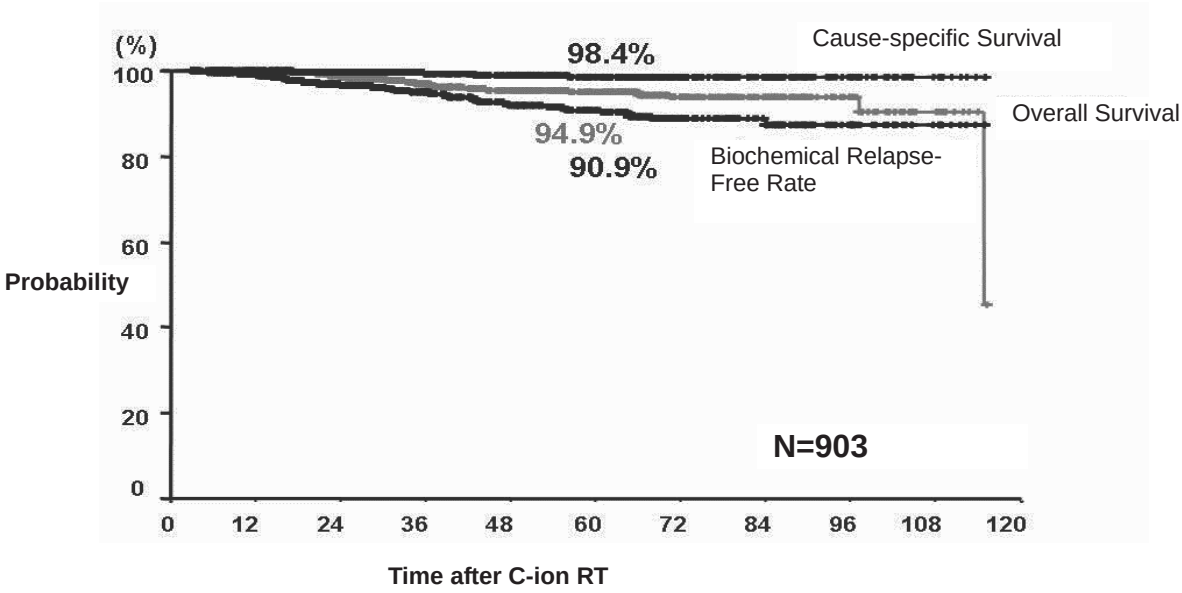


Table 2 is a risk grouped comparison of survival rate on large-scale clinical studies of combined therapy of X-ray therapy and endocrine therapy performed in the U.S. and the survival rate on carbon ion radiotherapy. The result shows that the survival rate is higher in the carbon ion radiotherapy in any groups.

Table 2. Comparing the Overall Survival Rate of C-ion RT with the Results of Meta Analysis of RTOG studies

Studies	Dose (Gy/fr.)	Overall Survival Rate					
		Group 2		Group 3		Group 4	
		No. pts.	5-y OS	No. pts.	5-y OS	No. pts.	5-y OS
RTOG Meta Analysis*							
RT alone	65-70/30-35	443	82%	338	68%	324	52%
RT + Hormone	65-70/30-35	114	76%	138	79%	103	63%
Carbon + Hormone	66-63/20 or 57.6/16	299	99%	210	93%	184	87%

*RTOG: Radiation Therapy Oncology Group; IJROBP 2000; 47(3): 617-627, Mack Toach III et al

4. Discussion

We introduced the treatment results of carbon ion radiotherapy in an established therapeutic approach after the phase II trial.

As for the treatment morbidity, in the lower urinary tract, the incidence was approximately the same in 63.0GyE/20 fractions carbon ion radiotherapy, intensity modulated radiation therapy and proton, which is interesting that it shows that this dose has comparable impact against lower urinary tract tissues. While for the 57.6GyE/16 fractions, the lowering of incidence was realized as a real outcome for shortening the treatment term. As for the rectal toxicity, even 63.0GyE showed lower rate than X-ray or proton, this is thought to be the proof of eminent dose convergence of carbon ion beam. In addition, 57.6GyE gained

further lowering. Adding shortening to the high dose convergence, significant reduction of toxicity was obtained.

Regarding the antitumor effect, especially in the high risk groups, high survival rate was gained. It is caused by the carbon ion's excellent curative effect along with the distinguished treatment strategy. There was no difference in relapse-free rate and survival rate between 20 fractions and 16 fractions, while the result showed that the toxicity was less in 16 fractions. Therefore reducing the fractions to 16 made it possible to achieve not only the improvement of efficiency but also the improvement of outcome from therapy.

5. Conclusion

Carbon ion radiotherapy is an ideal therapeutic approach as radiation therapy against prostatic cancer. Furthermore, regarding the point of both toxicity and curative effect, previous outcome strongly illustrated the fact. Shortening the treatment period also contribute to the better outcome, hereafter, further shortening and promotion of streamlining can be expected. Prostatic cancer is a target disease of therapy utilizing the characteristics of carbon ion beam, and prospected to have a great role in popularization of carbon ion radiotherapy.

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Clinical Experience of Carbon Ion Radiotherapy at GSI/Heidelberg

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Clinical Experience of Carbon Ion Radiotherapy at Hyogo

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Abstract

Hyogo Ion Beam Medical Center (HIBMC) was established in May 2001 as (1) the Japan's first local government-run charged-particle radiotherapy facility and (2) the world's first facility that provides both proton- and carbon-ion therapy. For the early period of 2001 to 2002, HIBMC conducted proton- and carbon-ion therapy on 30 patients each as part of the clinical trials for system approval. In 2003 HIBMC started to serve the public, and treated a total of 2,675 patients by the end of September 2010, including 885 patients receiving carbon-ion therapy. Recent statistics show that the number of patients undergoing carbon-ion therapy is increasing. Apart from prostate cancer, the numbers of patients undergoing proton- and carbon-ion therapy are almost equal. By tumor site, most of the cases treated at HIBMC relate to head and neck (28%), liver (25%), lung (16%), bone and soft tissue (11%), which account for 80% altogether. The treatment outcomes are mostly excellent. The HIBMC is treating an increasing proportion of patients with recurrent tumors and distant metastases, reflecting an increasing awareness of charged particle therapy among the patients attending general medical practice.

Introduction

Hyogo Prefecture launched the Hyogo Ion Beam Medical Center (HIBMC) plan as the flagship project of the '**Hyogo Anti-cancer Program**.' After 9 years of planning and construction, HIBMC started its operation in May 2001. HIBMC, located in the Harima Science Garden City, is divided into the radiotherapy ward (12,000 m^2) and the hospital ward (4,500 m^2). The radiotherapy ward comprises the ion source room, the accelerator system, and five treatment rooms. The 50-bed hospital ward includes consulting and treatment rooms, laboratories, cafeteria, and other facilities. This medical establishment has a beautiful Japanese garden, designed to be a place of comfort and respite for patients and visitors.

Before starting clinical trials for system approval, a series of physical and biological pre-clinical studies were performed on the radiotherapy system to confirm its safety and effectiveness. [1]Clinical trials were conducted on the proton radiotherapy in 2001, and on the carbon-ion radiotherapy in 2002. These clinical trials were required for the final step for filing the application for manufacturing approval of the treatment system, conducted based on the study protocols created according to the Good Clinical Practice (GCP) for Medical Device Trials. In late October 2002, the proton radiotherapy system was approved, and proton radiotherapy was made available to the public in April 2003. Later in January 2005, the carbon-ion radiotherapy system was approved, and HIBMC started to provide carbon-ion radiotherapy to local and regional patients in March the same year. The Ministry of

Health, Labour and Welfare approved the proton- and carbon-ion therapy under the Highly Advanced Medical Technology program in July 2004 and May 2005, respectively. The Highly Advanced Medical Technology program provides a partial reimbursement of the medical expenses for high-tech therapies under the national insurance system. The patient will bear the total cost of 2.883 million yen for undergoing the charged-particle therapy, while the rest of the medical expenses will be covered by the insurance program.

HIBMC is characterized as (1) the Japan's first local government-run charged-particle therapy center and (2) the world's first facility that provides both proton- and carbon-ion radiotherapy. This institution employs 43 full-time staff, including seven attending physicians, 11 radiological technologists, two medical physicists, one accelerator physicist, one pharmacist, 17 nurses, and 4 clerical workers. In addition, this center hires four part-time attending physicians, 17 contract technicians engaged in the operation, dosimetry, and quality assurance of the irradiation system, and seven contract clerical staff members taking care of the medical office procedures and post-treatment patient follow-up.

The HIBMC operating principles (hospital philosophy) are to: (1) improve cancer cure rate and encourage cancer patients to contribute to the community, (2) treat cancer at an early stage, (3) to create an 'un-hospital-like' relaxing atmosphere, (4) to create a hospital open to the whole world, and (5) to become a focal point for developing and disseminating state-of-the-art information on charged-particle therapy. In the sections below, the current status of HIBMC and the treatment results on major diseases as of September 2010 are described.

Methods

1. Radiotherapy System

The maximum acceleration energy of the HIBMC synchrotron is 230 and 320 MeV/u for proton- and carbon-ion beams, respectively. For carbon-ion radiotherapy, three treatment rooms are available, which are equipped with a variety of beam line configurations: 45-degree oblique beam line, horizontal and vertical beam lines, and horizontal beam line. For proton radiotherapy, two gantry rooms are also available in addition to these. The HIBMC accelerator system includes two ion sources, one RFQ linear accelerator, one Alvex linear accelerator, and one synchrotron. This system energizes carbon and protons up to 5 MeV/u by the RFQ and Alvarez linear accelerators. The particles are further accelerated and to the maximum of 320 meV/u by the synchrotron. Clinical application empoys 70 to 230 MeV/u proton beams with a water-equivalent path length of 40 to 300 mm, and 70 to 320 MeV/u carbon ions having a water-equivalent path length of 40 to 200 mm The accelerated particles are routed to the 45-degree oblique beam port (treatment room A), horizontal and vertical beam line ports (treatment room B), horizontal beam port (treatment room C), and two rotating gantries (treatment room G1 and G2). The gantry structure can be rotated in space around the patient, so that it can deliver proton beams from any direction. Irradiation beams pass through the irradiation field forming apparatus located in each treatment room before they reach to the patient (irradiation system). The irradiation field forming apparatus includes the ridge filter, collimator, range shifter, and bolus. The ridge filter is used to form the optimal spread-out Bragg peak (SOBP), the collimator is used to define the lateral irradiation field according to the shape of the target volume. The range shifter controls the position of the Bragg peak in depth inside the patient's body, and the bolus is set to optimize the path length. The beams are molded to fit the target volume, as they pass through these devices.

2. Treatment Criteria

We established our original treatment criteria, which provide guidelines for indications and treatment strategies. The in-house treatment criteria committee including specialists of various fields of oncology is convened at regular intervals to revise, amend, and update the criteria. The charged-particle therapy at HIBMC is basically indicated for solid tumors, particularly those involving the skull base, head and neck, lung, liver, prostate, bone and soft tissue. It is not generally indicated for cancers of the digestive tract, such as gastric and colorectal cancers, because these organs are mobile with peristalsis, and thus cannot be targeted correctly. Besides, it is not indicated for pharyngeal cancer, for which standard first-line treatment has been well established.

The longest path length of the carbon-ion beam of 320 MeV (maximum energy) is approximately 15 cm. This distance is not sufficient to cover the entire prostate gland from the lateral direction. Thus, prostate cancer is treated with proton beams.

3. Treatment Planning and Verification

Normally, it requires one week to complete the preparatory procedures for particle-ion irradiation, which includes creation of immobilization device, CT and MRI imaging, dosimetric evaluation by the treatment planning system, simulation, and pre-treatment evaluation of dose distributions. Specifically, the procedures include the following steps:

(1) The patient lies supine or prone on the flat treatment table. The patient is immobilized with a custom-made thermoplastic cast (Kuraray Shell Fitter F, Kuraray Trading Co., Osaka, Japan), with a size large enough for the irradiation field. The shell is fixed by means of pins to a carbon-fiber trunk fixation board (Taisei Medical Co., Ltd, Osaka, Japan) fitted on the table.

(2) Two-mm slice thickness plain x-ray CT (Toshiba Asteion CT port) and MRI (Philips Gyrosan Intera 1.5 T Master) images are taken for treatment planning, while the patient lies on the table with the immobilization device. Images are recorded from the vertex of the skull to the lower cervical region for patients with head-and-neck tumor; from the supraclavicular fossa to the periphery of the lower lung zone for patients with lung cancer; from 2 cm cranial to the diaphragm to the lower border of the liver for patients with hepatic cancer; and from the upper margin of the fifth lumbar vertebra to the perineum for patients with prostate cancer. In addition, breathing-synchronized CT scan images are acquired for the patients with liver and lung cancers.

(3) CT and MRI scans are transmitted online to the treatment planning system (Focus-M, CMS Japan Co. Ltd.).

(4) The contour lines of the gross tumor volume (GTV), clinical target volume (CTV), and organs at risk (OARs) are entered into the treatment planning system with reference to the x-ray CT and MRI images. The treatment-planning CT and MRI scans can be fused by using the image fusion processing technique (Focal, Japan Co. Ltd.).

(5) The planning target volume (PTV) is created by expanding the CTV with an appropriate margin required for the target lesion, according to the three-dimensional treatment-planning CT scans.

(6) Based on the three-dimensional CT-based simulations, beam directions are optimized for the tumor’s anatomical location and the degree of its invasion. The dose distribution is calculated taking note of the penumbra region (proton: 5 mm; carbon ion: 2 mm). Attention must be paid to limit the dose estimates for the normal tissues of the crystalline lens, brain, spinal cord, lung, liver, kidney, gastrointestinal tract, and other

organs below the tolerable dose. In order to grasp the dose relationships between CTV, PTV, and OARs, the dose-volume histograms (DVHs) are created.

(7) The treatment planning system automatically determines the wobbler radius and SOPB, as well as the scatterer, ridge filter, and range shifter parameters for each port. Data on the collimator and bolus manufacture, port-specific radiation dose, and the digitally reconstructed radiographs (DDRs) to be used for checking at the irradiation system are created, and transferred to the manufacturing device and the irradiation system.

A dummy run is performed one day before the first real session to reduce the patient's nervousness, verify the patient fixation, confirm the correct transmission of various parameters, and obtain reference image data. Reference images refer to the bidirectional (frontal and lateral) x-ray DRR and BEV images acquired by using the treatment system. After verifying that these coincide with the images already transferred from the treatment planning system, the reference images are stored on the irradiation system server. The reference images are used for patient positioning at each irradiation session.

The number of treatment sessions varies from four to 38, depending on the tumor size and location. In the early period following the opening of HIBMC, the treatment plans were determined by the physician alone. At present, clinical groups consisting of radiological technologists, medical physicists, and physicians take charge of developing the treatment plans for proton- and carbon-ion therapy, and the plans are reviewed and authorized at the treatment planning conferences convened every working day. In order to assess the agreement between the dose estimates and measurements, dose distributions are determined for each portal using water phantom before initiating the actual session. The dose distribution is checked immediately after the first irradiation session, taking advantage of the autoactivation phenomenon. That is, autoactivation PET images are taken by using PET camera following the completion of the initial treatment session, and the results are compared with the treatment planning images for consistency.

4. Follow-up

Conventional type of patient follow-up system is inappropriate for many particle-ion radiotherapy facilities that treat patients from various different places, both near and distant. Hence, the HIBMC organizes the specific medical teams consisting of the attending physician, nurse, and clerical staff members. After completion of the treatment at HIBMC, the patient is delivered the patient file folder containing the documents and materials concerning his or her own medical history, particle-ion radiotherapy, isodose charts, blood and urine test results, tumor scan images (CT, MRI), completed patient interview sheets, and communication sheets. This patient file folder functions as the central means for the follow-up communication between the patient and the treatment staff of HIBMC. This folder (as well as its contents) is generally kept by the patient and used for his or her health management purposes. The folder contains all information pertaining to the medical treatment performed at HIBMC. It assists the patient to grasp the post-treatment course of disease by reviewing the diagnostic images and blood test results. If the patient newly undergoes a medical examination, he or she will send the results along with the file to HIBMC. The received new data (e.g., hard copy films) will be electronically stored at the follow-up observation room. After the new data are entered into the patient's medical chart, all the materials will be sent back to the patient's residence. Since the follow-up does not generally involve face-to-face consultation, the attending physician makes effective use of the interview sheets, communication sheets, photographs of the patient's skin, and other relevant materials to supplement the lack of direct communication and contact. The

physician requests the patient to visit the clinic in case of a significant event in order to see the patient in person. The patients are welcome to make phone calls to the follow-up nurse and physician for consultation, as appropriate. Since this system is functioning effectively for our center, the number of patients lost to follow-up is close to nil.

Results

1. Trend in Annual Numbers of Radiotherapy Treatments

The HIBMC treated 30 patients by proton radiotherapy in 2001, and another 30 patients by carbon-ion therapy in 2002. These patients received medical treatment as part of the clinical trials for system approval. The HBMC started to serve the public after the advanced therapeutic system was authorized by the Ministry of Health, Labour and Welfare in 2003. A total of 3560 patients with tumors were treated at HIBMC by the end of September 2010. The HIBMC started offering proton radiotherapy to the public since 2003, and the cumulative number of treated patients has reached 2675 so far. (The total number of patients treated at HIBMC from 2001 is 2735.) Carbon-ion radiotherapy was started in 2005. A total of 885 patients have been treated so far (since 2003, Figure 1). The annual numbers of patients receiving radiotherapy show an upward trend, with the exception of FY 2008. We treated 636 patients in FY 2009, though the final financial reports for this year failed to end in the black on a one-year budget basis. During the first half (April to September) of FY 2010, 345 patients underwent radiotherapy. It is predicted that the annual budget will turn into black for the first time, if this trend continues.

Recent statistics show that the number of patients undergoing carbon-ion therapy is increasing. Apart from prostate cancer, the numbers of patients undergoing proton- and carbon-ion therapy are roughly on the par with each other.

Hyogo Ion Beam Medical Center (HIBMC)
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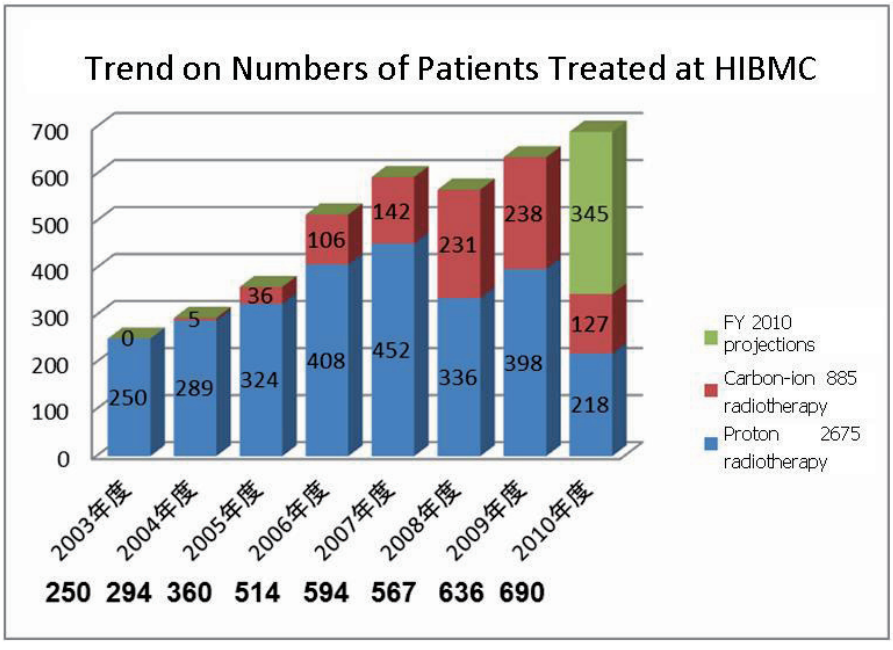

Figure 1. Trend on Annual Numbers of Patients Treated at HIBMC by Particle Type: From 2003 (Start of Operation) to September 2010

By type of treatment, 88% of the patients underwent definitive therapy (including semi-definitive treatment), while the remaining 12% received palliative therapy (including symptomatic treatment). When analyzed by year, the proportions of patients treated with palliative therapy are gradually increasing. The analysis of tumor type showed that 75% of the patients were fresh case, whereas 25% had either recurrence or distant metastasis, and the proportions of patients with recurrence and distant metastasis are gradually rising (Figure 2).

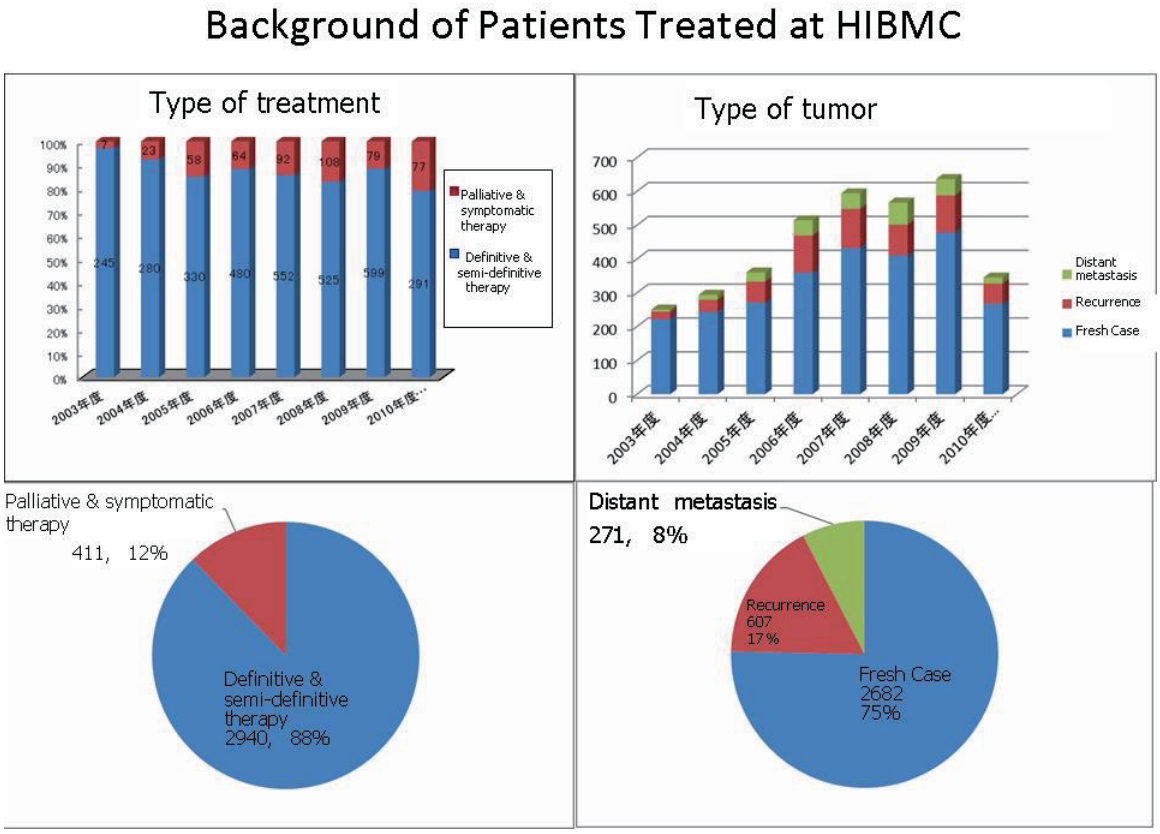

Figure 2. Breakdown of Patients Treated with Particle-ion Radiotherapy at HIBMC: By type of therapy and tumor

Figure 3 graphically represents the breakdown of 915 patients that underwent carbon-ion radiotherapy at HIBMC (including 30 patients treated in the 2002 clinical trial). By tumor site, most of the cases treated at HIBMC related to head and neck (255 patients, 28%), liver (224, 25%), lung (145, 16%), bone and soft tissue (103, 11%), which account for 80% altogether (Figure 3).

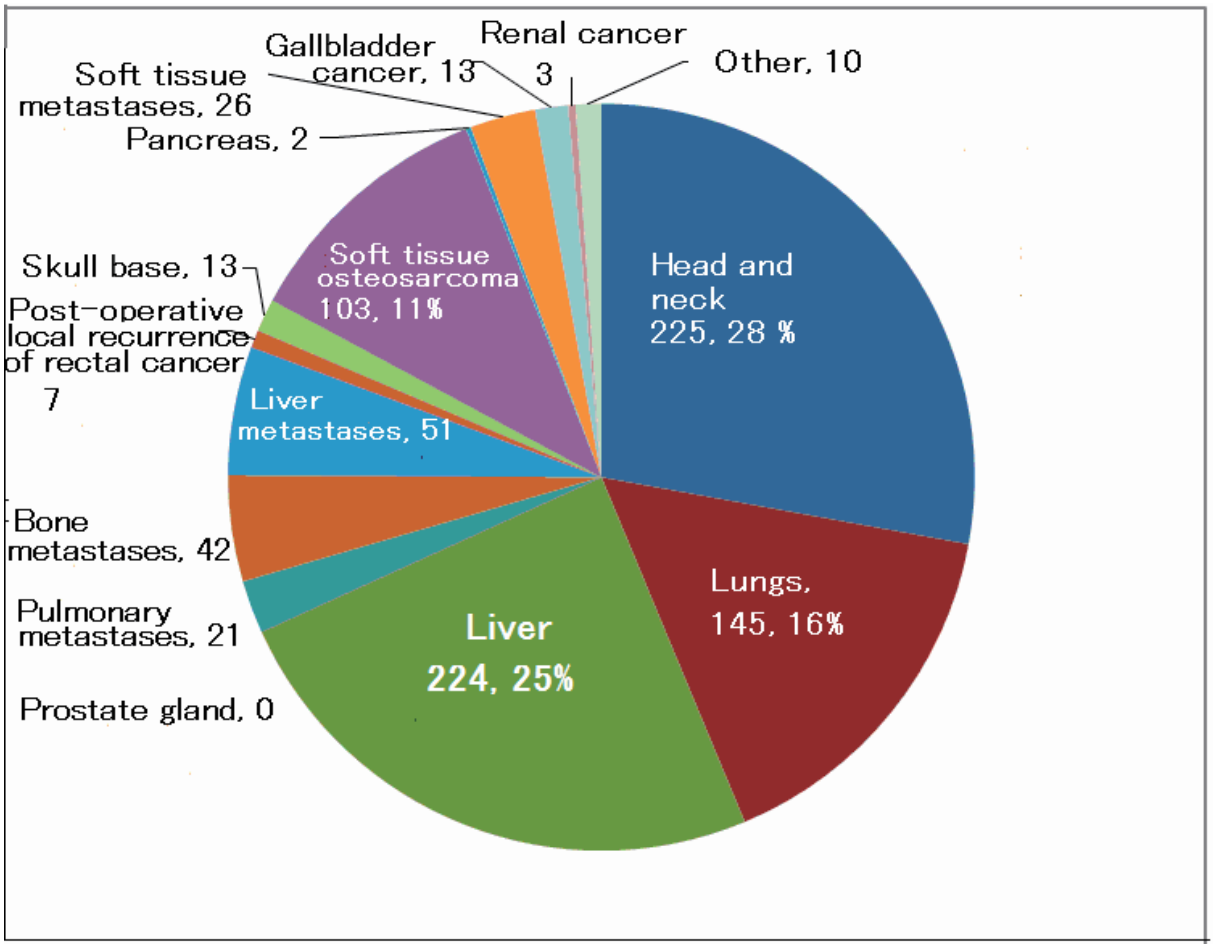

Figure 3. Breakdown of 915 Patients Treated with Carbon-ion Radiotherapy for the Period of 2002 to September 2010.

2. Treatment Outcomes for Carbon-in Radiotherapy

The following summarizes the latest results of analysis on the treatment outcomes at HIBMC:

(1) The head-and-neck tumors included the following primary sites in descending order of frequencies: nasal cavity (31%), maxillary sinus (10%), oral cavity (10%), major salivary gland (10%), pharynx, and paranasal sinus. By type of tissue, they included the following: malignant melanomas (31%), adenoid cystic carcinomas (18%), squamous cell carcinomas (13%), adenocarcinomas (11%), and sarcomas (10%). A large proportion of these tumors were presumably radioresistant non-squamous cell carcinomas. When classified by the degree of stage at first visit, a significant majority of patients had locally advanced T3 (24%) and T4 (45%) tumors. Eighty-six percents did not have lymph node metastases. The largest proportion of the patients received a dose of 57.6 GyE in 16 fractionations (45%), followed by 70.2 GyE in 26 fractions (26%) and 60.8 GyE in 16 fractions (19%). The carbon-ion radiotherapy outcomes for 62 malignant melanoma patients showed a 57% 2-year overall survival, 20% 2-year relapse-free survival, and 78% 2-year local control rate.

(2) For lung cancer, the primary target patient population was stage-I patients. In addition, T3 and T4 cancers including pancoast tumors were also eligible for carbon-ion therapy. For 23 stage-I patients treated with 52.8 GyE in four fractionations, the 3-year overall survival rate was 82%, and the 3-year local control rate was 68%. For T1N0M0 (IA) and T2N0M0 (IB) cancers, the 3-year overall survival rates were 87% and 75%, and the

3-year local control rates were 70% and 63%, respectively.

(3) Most of 140 liver cancer patients were treated with 52.8 GyE in four fractionations (57%) and 66 GyE in 10 fractionations (21%). For these patients, the 5-year local control rate was 90%, and the 5-year overall survival rate was 36%. These results were comparable, or superior to the outcomes for surgical resection and radiofrequency ablation.

Discussion

At HIBMC a larger number of patients have been treated with proton radiotherapy than carbon-ion radiotherapy. The gap is attributable to the facts that carbon-ion radiotherapy was started two years later than proton radiotherapy, the rotating gantries are available only for proton radiotherapy, and carbon-ion therapy cannot be used for the treatment of prostate cancers and other deep-seated tumors, because the carbon-ion beams with a maximum energy of 320 MeV cannot sufficiently reach them (maximum path length: 15 cm). Only a very small number of patients received carbon-ion radiotherapy during the early period following its start in 2005. In 2007 we started to create treatment plans by applying both treatment options for all patients except for those with prostate cancer. This change in treatment strategy gradually increased the numbers of patients receiving carbon-ion radiotherapy. At present, fairly equal numbers of patients are treated by these modalities. The collimated carbon-ion beams have much smaller beam scattering than protons, and therefore possess much sharper dose localization profiles. For these reasons, carbon-ion beam is superior to proton beam in terms of dose restrictions for OARs and dose coverage to the target tumors. Thus, carbon-ion radiotherapy is being chosen more and more frequently.

The head-and-neck region is packed with several critical organs and tissues involved in audiovisual, gustatory, and olfactory perceptions, as well as speech, manducation, deglutition, and other functions that are necessary to maintain human life. These lie adjacent to the skull base supporting the brain. Carbon-ion beam, with its excellent dose localization profile, has an advantage for delivering a large amount of radiation focused on the tumor, while leaving optic nerves and other OARs intact[23]. Head-and-neck tumors include not only lymphomas and squamous cell carcinomas that are sensitive to conventional x-ray radiotherapy and chemotherapy, but also a wide variety of radioresistant tumors such as adenocarcinomas, adenoid cystic carcinomas, malignant melanomas, and sarcomas. The particle-ion radiotherapy has a potent biological effect on radioresistant tumors, offering a great clinical benefit.

Surgical elimination is standard treatment for stage-I lung cancer. Therefore, definitive charged particle radiotherapy is indicated for elderly patients and patients with unresectable cancer among those with stage-I lung cancer. [4]One major issue to note in planning treatment for lung cancer is that the lung contains large low-density regions (filled with mostly air); of note is the fact that it is more difficult to stop beams at specific sections of the lung than at desired spots of the liver and other solid organs. In order to completely cover the entire tumor mass of the lung, the SOBP should be optimized to include the thoracic wall. In addition, use of a bolus leads to a scattered dose distribution and low tumor dose, due to the large difference in density between the tumor and the peri-tumoral normal lung tissue. Protons have poorer dose localization characteristics than carbon ions, again proving the clinical superiority for the latter.

Since the liver is a solid organ, it is much easier to control and deliver charged particle beams on the liver than lung. However, depending on the location of the tumor, the irradiation field may comprise part of the OARs, such as the skin, stomach, duodenum, colon, and kidney. It deserves particular attention that a high dose

irradiation on the upper gastrointestinal tract will inevitably result in peptic ulcer. Large liver cancers may often involve late adverse reactions, such as rib fracture, dermatitis, pleuritis, and pleural effusion. Liver cancer treatments include a variety of procedures including surgical resection, hepatic arterial embolization, intra-hepatic arterial infusion chemotherapy, percutaneous ethanol injection, and radiofrequency ablation. Liver cancers are characterized by specific features that are not seen in other types of solid tumors; many liver cancer patients present damaged hepatic function due to the underlying liver cirrhosis, and a new liver cancer may often develop post-operatively in patients with a well-controlled single lesion because multiple discrete lesions in the liver are left untreated. Accordingly, the suitable local therapy should preferably be a highly curable and low-invasive method that will prevent the treatment-induced hepatic damage from interfering with the subsequent medical treatment. This underscores the promising therapeutic potential of charged particle radiotherapy. We compared the latest treatment results of carbon-ion radiotherapy performed at HIBMC with those of radiofrequency ablation and surgical resection. The comparison indicated that carbon-ion radiotherapy is equal, or superior to other modalities of treatment (Tables 1, 2).

The HIBMC is receiving an increasing proportion of patients with recurrent tumors and distant metastases, which is suggestive of the growing recognition of charged particle therapy among patients attending general medical practice. It is the author's belief that charged particle radiotherapy should need to be actively promoted.

Table 1. Comparison of the Results of Liver Cancer Treatment by Carbon-ion Radiotherapy, Radiofrequency Ablation, and Percutaneous Ethanol Injection Therapy

報告	n	腫瘍最大径(cm)	局所再発率(%)	全生存率(%)
Lencioni et al. 2003 Italy	PEIT: 50 RFA: 52	Mean: 2.8 Mean: 2.8	18 **9**	(2-yr) 88 **(2-yr) 98**
Lin et al. 2004 Taiwan	PEIT: 63 RFA: 62	Mean: 2.3 Mean: 2.5	11.9 **3.9**	(3 yrs) 51 **(3 yrs) 74**
Shiina et al. 2005 Japan	PEIT: 114 RFA: 118	Mean: - Mean: -	11.4 **1.7**	(4 yrs) 57 **(4 yrs) 74**
HIBMC(初発例、<3cm)	18	Mean: 2.3	5.9	(2 yrs) 94 (3 yrs) 94 (4 yrs) 81
HIBMC(全症例、<3cm)	67	Mean: 2.5	1.4	

Table 2. Comparison of the Results of Liver Cancer Treatment by Carbon-ion Radiotherapy and Surgical Resection

報告	n	Child-Pugh	Mortality	1 year (%)		3 years (%)		5 years (%)	
				OS	DFS	OS	DFS	OS	DFS
Shuto et al. 1998 Japan	264	A: 94.7% B: 5.3%	In-hospital: 3%	89	78	82	40	50	25
Fan et al. 1999 China	211	-	In-hospital: 9.5%	67	60	50	38	37	27
Belghiti et al. 2002 France	300	A: 94% B: 6%	In-hospital: 6.4%	81	71	57	51	37	32
Kanematsu et al. 2002 Japan	303	A: 69% B: 30% C: 1%	In-hospital: 3.3%	84	75	67	41	51	27
HIBMC (初発例) 切除可能群	27	A: 86% B: 14%	0%	92	75	69	45	59	15
HIBMC (初発例) 切除不可能群	20			90	64	78	42	78	21

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Clinical Trial of Tumor Therapy with Carbon Ions at Heavy Ion Research Facility in Lanzhou (HIRFL), IMP, China

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Background

Since November 2006, the carbon ion radiotherapy (RT) has been performed within a clinical pilot project at the Heavy Ion Research Facility in Lanzhou (HIRFL), Institute of Modern Physics (IMP), Chinese Academy of Sciences, China, collaborating with the General Hospital of Lanzhou Command, Tumor Hospital of Gansu Province.

Patients and Methods

Between November 2006 to November 2010, 126 patients and have been treated at the HIRFL of IMP, Lanzhou, China. In the 126 patients, there were 103 with superficially-placed tumors (squamous cell carcinoma of the skin, basal cell carcinoma of the skin, malignant skin melanoma, sarcoma, lymphoma, breast cancer, metastatic lymph nodes of carcinomas and other skin lesions) and 23 with deep-steaded tumors (hepatocellular carcinoma, brain tumor, sacrum chordoma, bone and soft-tissue sarcomas, head and neck tumors, pelvic mucinous adenocarcinoma and malignant melanoma). The majority of patients were with failures or recurrences of conventional therapies. All patients had histological confirmation of their tumors before irradiation**.** There were 75 males and 51 females, and median age at the time of radiotherapy was 53.7 years (range 1–88 years). Karnofsky Performance Scale (KPS) was more than 70 for all patients. They received total doses of 40–75 GyE with a weekly fractionation of 7 × 3-15 GyE/fraction.

There are two heavy ion RT terminals at the HIRFL of IMP, China, including one with vertical beams and passive beam delivery system for superficially-placed tumors and another one with horizontal beams and both passive and active beam delivery systems for deep-seated tumors [1, 2]. The carbon beams with the maximum energy of 100 MeV/u and 250 MeV/u were used for superficially-placed and deep-seated tumors RT, respectively. Treatment planning system (TPS), which was developed by IMP, was used to calculate the parameters of the irradiation system, the dose optimization and dose distribution for all patients. Two and three-dimensional conformal layer-stacking irradiation methods [1] were used within the carbon ion RT. Beam weights (physical absorbed doses) of each Bragg peak are optimized by iterative technique or genetic algorithm. Broad beam algorithm based on ray-tracing technique was used for dose distribution calculation in the TPS.

Patients were immobilized with a vacuum cushion or a head mask during treatment, allowing a positioning accuracy of less than 2 mm. Target volume was defined by physical palpation, ultrasonography, CT and MRI scans. The clinical target volume (CTV) was defined as the gross total volume GTV with a 0.5-1.5 cm margin

axially. RBE of 2.5-3 within the target volume was used in the trial. The radiobiological effective dose is expressed in GyE, which is = RBE × physical dose.

Patients had follow-up examinations were performed 1 month after treatment, in 3-6 month intervals for the first 2 years and annually thereafter. Local control rates were estimated according to WHO criteria. The evaluation included a physical palpation, ultrasonography, CT, MRI scans and a complete blood count. Local control rates and survival rates were calculated using Kaplan-Meier methods. Acute and late side effects were scored according to the Common Toxicity Criteria (CTC). Reactions occurring during RT or within the first 3 months after RT were scored as acute reactions.

Results

The mean follow-up for patients with superficially-placed tumors was 24 months with ranging from 12-36 months. The tumors responded very well to the treatment in all patients. Up to 3-6 months, majority of tumors disappeared completely or almost. The actuarial local control and overall survival rates rates for 103 patient with superficially-placed tumors were showed in Figures 1 and 2, respectively. Figures 3 and 4 show separately the follow-up photos of patients with squamous cell carcinoma and basal cell carcinoma of the skin. The tumors also responded well to carbon ion RT in 23 patients with deep-seated tumors. No severe side-effects > CTC grade III have been observed.

Fig. 1. Kaplan-Meier Curves of Actuarial Local Control

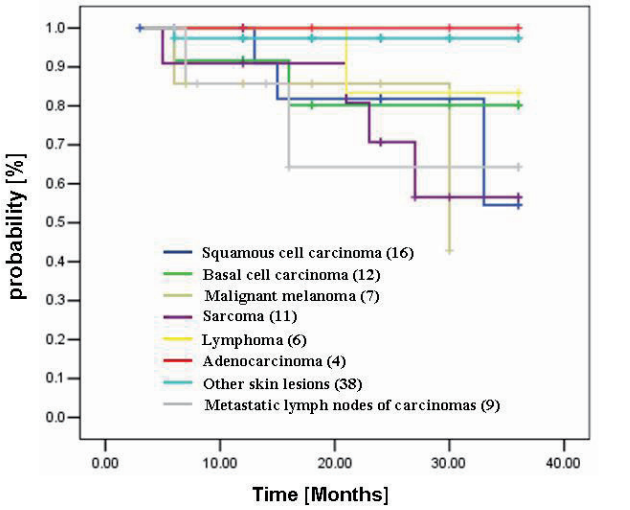


Fig. 2. Kaplan-Meier Curves of Actuarial Overall Survival

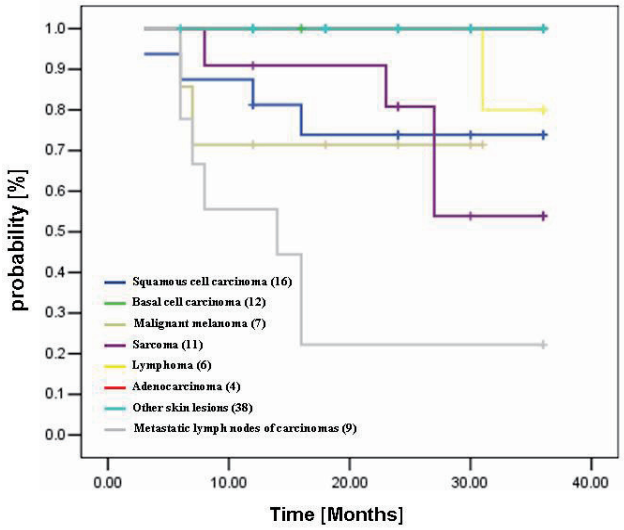


Fig.3. A 42-year-old woman with skin squamous cell carcinoma of the right foot. She has been alive for 46 months after carbon ion radiotherapy of 70.4GyE/9 fractions

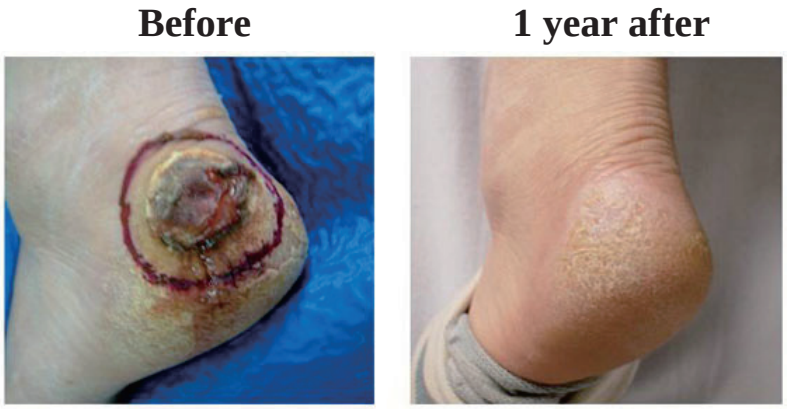
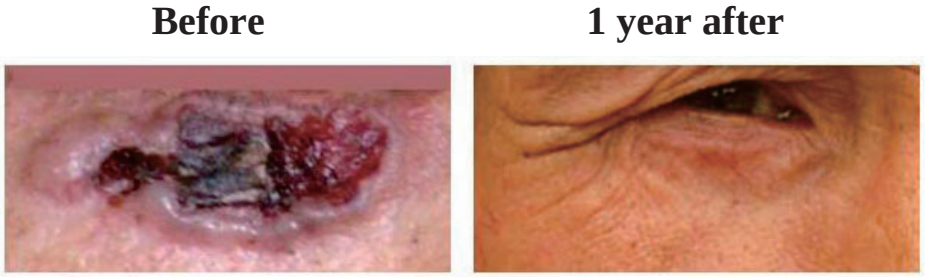


Fig.4. A 68-year-old man with skin basal cell carcinoma of the right lower eyelid (postoperative local recurrence). She has been alive for 46 months after carbon ion radiotherapy of 55GyE/11 fractions.



Conclusions

The data demonstrated that demonstrated that heavy ion radiotherapy at HIRFL, IMP is clinical effective and safe, especially for patients with failures or recurrences of conventional therapies, although the follow-up was short.

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Carbon Ion Radiotherapy at Gunma University

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Abstract

Carbon ion radiotherapy for the first cancer patient at Gunma University Heavy Ion Medical Center (GHMC) was initiated with concise medical heavy ion accelerator in March of 2010. The size and cost of the facility were approximately one-third of HIMAC of NIRS while keeping its high treatment performance. By January 2010, a total of 92 cancer patients have been treated with carbon ion radiotherapy at GHMC including 76 prostate cancers, 7 lung cancers, 4 liver cancers, 3 bone & soft tissue sarcomas, and 2 head & neck cancers. Most of the patients were treated with 16 fractions over 4 weeks except for those with lung and liver cancers were treated with 4 fractions over one week. Both acute and late reactions of the patients were minimal with equal or less than Grade 2 so far in the short follow-up period. The clinical indications, the recent clinical status, and the future direction of GHMC are introduced.

Materials and Methods

Facility: Our facility is the first hospital-based facility in Japanese universities and was funded by the Japanese and local governments. It is a prototype of a concise medical heavy ion treatment facility designed for commercially available facility able to distribute nation-widely (Figure 1, 2). The size of the building is 60m x 45m square and 15m in height. The major specifications of the facility were determined based on the experience of clinical treatments at the NIRS. The main accelerator is a slow-cycling synchrotron with 20m in diameter, and it accelerates carbon ions to an energy range from 140 to 400 MeV per nucleon with dose rate of 5GyE/mimute which has actuarial penetration of 25cm in water. A spiral wobbler system and beams with spread out Brag peak（SOBP） consist of the passive beam delivery system which enables to treat moving targets safely with gating irradiation system. In addition, more advanced beam delivery by stacking layer method has been introduced to create superior dose accumulation to targets. The facility has 4 treatment rooms consisting of one with a fixed horizontal beam line, one with a fixed vertical beam line, one with both fixed horizontal and vertical beam lines, and the remaining one for research and development of advanced scanning techniques for targeting small lesions. Especially, in the 4^{th} room, a precise 3D spot scanning beam port will be installed by March 2011 for experiment of micro-surgery radiotherapy. MRI and PET/CT are equipped for treatment planning and verification of dose distribution. The actual dose deposition is verified using PET/CT by the visualization of secondary positron distribution generated by fragmentation of projectile carbon beams. The CdTe Compton camera is being developed for the visualization of beam deposition more accurately by detection of the secondary gamma rays of projectile carbon beams.

Figure 1. Gunma University Heavy Ion Medical Center (GHMC)

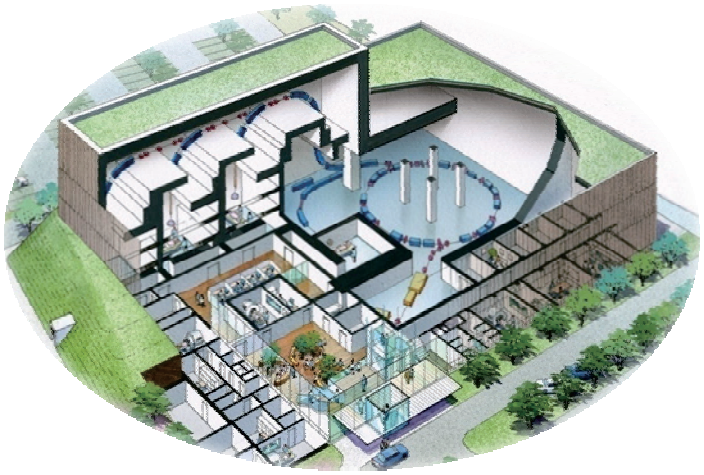

Figure 2. Birds eye view of GHMC

Clinical indications at Gunma University

First cancer patient received carbon ion radiotherapy at Gunma University was in March of 2010. In GHMC, the clinical results of carbon ion radiotherapy at NIRS in each tumor site were reviewed for the efficacy and safety and then currently best available dose and fractionation schedules were decided for our clinical protocols with reference to those of NIRS (Table 1). In brief, the primary objective of our clinical study was set as to confirm and prove the efficacy and reproducibility of the outstanding results of carbon ion radiotherapy at NIRS. Basically most of the tumors were treated with 16 fractions over 4 weeks but for lung cancer and liver cancer being with 4 fractions over one week.

Table 1. Ongoing clinical protocol at Gunma University Heavy Ion Medical Center

Site (protocol #)	Eligible patients	Treatment
Lung cancer (GUNMA0701)	・Histologically proven non-small cell lung cancer ・T1a-T2aN0M0 (peripheral type,TNM classification, 2009) ・Inoperable or decline surgery	*T1a-b:* 52.8 GyE/4 fr/1 week *T2a:* 60.0 GyE/4 fr/1 week
Prostate cancer (GUNMA0702)	・Histologically proven prostate cancer ・T1c-T3N0M0 (TNM classification, 2002) *Low risk group:* PSA <10ng/mL and Gleason score ≤6 and T1c-T2b N0 M0. *Intermediate risk group:* Other than low risk and high risk groups *High risk group:* PSA ≥20ng/mL or Gleason score ≥8 or T3 N0 M0	*Low risk group:* Carbon ion RT alone (57.6 GyE/16 fr/4 weeks) *Intermediated risk group* Hormone therapy (6-8 months) and carbon ion RT *High risk group* Hormone therapy (2 years) and carbon ion RT
Liver cancer (GUNMA0703)	・Histologically proven or compatible feature on CT/MRI with hepatocellular carcinoma ・Single lesion ・No invasion of main trunk of the portal vein ・T1-3N0M0 (TNM classification, 2002) ・Child-Pugh A or B	52.8 GyE/4 fr/1 week
Rectal cancer (GUNMA0801)	・Recurrent pelvic tumor after surgery for rectal cancer ・No metastatses other than pelvic tumor ・Curative intent for primary surgery	73.6 GyE/16 fr/4 weeks
Head and neck cancer (GUNMA0901)	・Histologically proven non-squamous cell carcinoma ・TanyN0M0 (TNM classification, 2002)	64.0 GyE/16 fr/4 weeks
Bone and soft tissue sarcoma (GUNMA0904)	・Histologically proven bone and soft tissue sarcomas ・Stage IA-III (TNM classification, 2002)	*Standard:* 70.4 GyE/16 fr/4 weeks *Sacral chordoma:* 67.2 GyE/16 fr/4 weeks *Spine tumor:* 64.0 GyE/16 fr/4 weeks

Results

From May 2010 to December 1, a total of 92 cancer patients including 76 prostate cancers, 2 head & neck cancers, 7 lung cancers, 4 liver cancers, 3 bone & soft tissue sarcomas have been treated with carbon ion radiotherapy at GHMC. The acute reaction of patients was minimal with equal or less than Grade 2 . In addition, there is no late complication severer than Grade 2 in various normal tissues. Up to now and with the current short follow-up period, carbon beam therapy in GHMC has been undertaken safely and on-scheduled without any major problem.

Discussion

This is the first carbon ion radiotherapy facility in a university hospital funded by the Japanese government and local government. Gunma University started heavy ion therapy project in 2001. Then Gunma University collaborated with NIRS for the designing and R&D developing a concise therapy facility for nation-wide distribution in 2004. In 2007, the construction of the building was started. In August 2009, C-ions were transported into a treatment room within a month of adjustment after injection of the beams and commissioning for treatment, carbon ion radiotherapy for the first cancer patient at GHMC was initiated on time in March of 2010. The total amount of instruction cost is about 80-90M Euros by the currency exchange rate. The expected number of patients to be treated is about 600 per year in coming years.

In order to spread heavy ion therapy nation-wide, the small-sized and less expensive machine must be developed. For this purpose, the ion source was only carbon so that the cost and the size of this facility could be decreased to one third of HIMAC in NIRS. There are three treatment rooms and the performance of the accelerator is comparable to or even better than HIMAC in Chiba. Furthermore, an additional room was designed for the purpose of academic research and development. As the first facility of the nation-wide distribution of carbon ion therapy, Gunma University has the mandate of training the personnel, such as radiation oncologists and medical physicists for the nation-wide distribution.

Gunma University also has the duty of developing more sophisticated machines and treatment modalities. Our treatment facility is concisely-sized and has high-performance capability. As described, our accelerator is only aimed at medical use with practical benefits so that generating beam is specialized to only carbon beam, and the maximum energy and intensity of carbon beams are determined to be 400MeV/n with dose rate of 5GyE/mimute which has actuarial penetration of 25cm in water. In addition, 3 treatment rooms are designed, which are enough for treating about 600-800 patients per year as proven by experience of HIMAC. Our machine will introduce 3D beam delivery system called stacking layer method which creates more desirable dose co formality with one port. For precise treatment, the facility has been equipped with respiratory gating tool for moving target of lung cancer and liver cancer, and PET/CT for verification of the real dose deposition by the visualization of secondary positron distribution generated by fragmentation of projectile carbon beams.

In addition, there is another room for the research and development for high precision heavy-ion microsurgery system. This technique is to create carbon beams of 2 to 3mm in diameter and to irradiate a minute targets in the body with positional accuracy of less than 1 mm. This technique will be applied to various diseases such as brain pituitary and spinal cord or vertebral tumors, vascular lesions such as AVM, and eye diseases.

The promising clinical outcomes have been reported from many of phase I/II and phase II studies for various tumor sites carried out at NIRS. The primary objective was set as to achieve similar the outstanding results of carbon ion radiotherapy at NIRS and confirm and prove the efficacy of carbon ion radiotherapy by the concise medical heavy ion radiotherapy machine. Hence, we reviewed NIRS results in terms of the efficacy and safety of

carbon ion radiotherapy in each tumor site. Then currently best available dose and fractionation schedules obtained at NIRS were adopted for our clinical protocols in GHMC. Up to now and with the current short follow-up period, carbon beam therapy in GHMC has been undertaken safely and on-scheduled without any major problem as mentioned above. However, there is a need of multi-institutional clinical study on carbon ion radiotherapy in order to prove the clinical effectiveness with establishing nation-wide powerful evidence to stakeholders. Therefore, at present, a prospective study of prostate cancer is under preparing among all proton and carbon ion radiotherapy facilities in operation in Japan. In this study, prostate cancer patients with same eligibility will be treated with proton or carbon ion beams in each prescribed dose and fractionation. The GHMC will take part in this clinical study.

Conclusion

Carbon ion radiotherapy started for various cancer patients at GHMC by the concise facility in March of 2010 and a total of 92 cancer patients leading 76 prostate cancers and 7 lung cancers have been treated by January of 2010. The treatment is launched safely so far with minimal acute and late reactions of normal tissues.

Current Status of CNAO

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Abstract

In the Foundation CNAO, the accelerator complex installed already and commissioning between them were started and completed site by site. Proton beams are coming to the treatment room. Protocol for clinical experimental activities was autholozed on the 1st of October 2010 by Minister of Health. After the confirmation and permission from ethical comittee, clinical studies using proton and carbon ions will start. The studies around CNAO project, including PARTNERS (Particle Training Network for European Radiotherapy), ULICE (Union of Light Ions Centres in Europe), MISHA (Multicharged Ion Source for Hadrontherapy), PRR (Proton Range Radiography), NST (Nuclear Scattering Tomography), IHI (Interaction Vertex Imaging) and In-beam PET, are ongoing and revealing the results.

Introduction

The *Centro Nazionale di Adroterapia Oncologica* (National Center for Oncological Hadrontherapy, CNAO) is the first Italian facility for the treatment of deep located tumors with proton (u to 200 MeV/u) and carbon ion (up to 400 MeV/u) beams and active raster scanning technique [1]. The accelerator complex includes a synchrotron and three treatment rooms with fixed horizontal and vertical beam lines (Fig. 1).

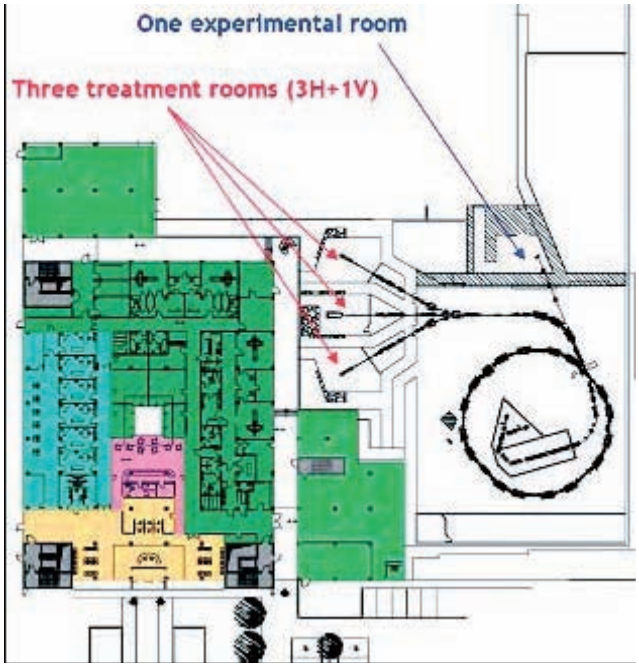

Fig. 1: Accelerator complex in CNAO

Methods and Materials

CNAO beams are generated by two ECR sources, able to produce both particle species, and transferred to a RFQ and a LINAC through a Low Energy Beam Transfer line (LEBT) at 8 keV/u and then accelerated up to 7 MeV/u before being injected in the synchrotron ring with maximum energy of 400 MeV/u.

In one of the three treatment rooms, a vertical and a horizontal fixed beam lines are provided, while in the other two rooms the treatment will be administered with horizontal beams.

The treatment rooms are being equipped with newly designed systems for patient setup and monitoring (Fig. 2), including 1) patient preparation in a dedicated area, 2) transport inside the bunker and 3) automatic positioning (PPS) to be managed by infrared optical tracking (OTS) and X-ray imaging (PVS).

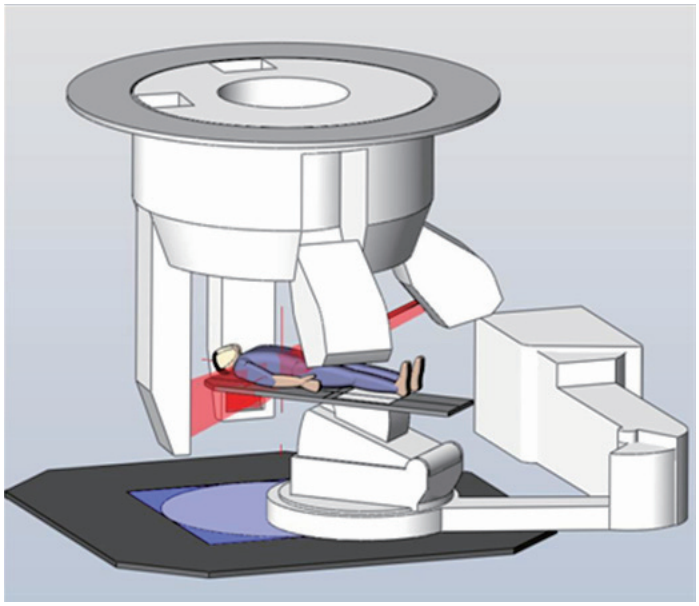

Fig. 2: Patient positioning and verification.

In the first phase, CNAO will focus on head and neck cancers, bone and soft tissue sarcomas and skull base tumors.

Results

The injector was fully commissioned by the end of 2009. Full installation of the machine was completed in early 2010. Linac beam commissioning was successfully concluded by the CNAO-GSI-INFN collaboration and design beam currents were achieved [2]. Finally, twenty CNAO staff members were trained in linac operation in November 2009 – marking the end of the GSI services fixed in the CNAO-GSI contract. First turn in the synchrotron was demonstrated on December 2009. On 17th of September, 2010, first proton beam accelerated to 60 MeV and followed acceleratio to 250 MeV. First beam in the tratment room extracted on the 15th of October 2010.

Authorization to clinical experimental activities obtained on the 1st October 2010 from “Minister of Health”, which will continue 18 months and number of patients to be treated is 230 (80 with protons and 150 with carbon ions). The ethical committee has been organized on November 2010 and will be ready for the discussion of clinical protocols. Patients referred abroad have been exceeded over 28 patients during the past 4 years. In

coopearation with NIRS, 1) conversion of equivalent doses, 2) original methodology and 3) simulation in simple geometries and real patients anatomy (comparison of hundreds of plans) are undergoing.

In medical physics, the protocol for beam commissioning and the study of immobilization devices to be employed are started. Additionaly, installation of 3 Tesla MR scanner (Imaging), introduction of OIS Elekta Mosaiq with specific adaptations (Information Technology), inplementation of Siemens Syngo PT version VA11 (treatment planning), starting up of hardware models for the commissioning between physical and dosimetric TPS (Monte Carlo simulations) and the testing of dosimetric devices have been commenced.

Discussion

There are a lot of cooperative studies between CNAO and corresponding institutions, concerning about the accelerator complex and clinical protocol, in domestic and international area, which are listed below.

National corresponding institutions

TERA Foundation: final design and high tech specifications

INFN: co-direction HT, technical issues, radiobiology, research, formation

University of Milan: medical coordination and formation

University of Pavia: technical issues, radiobiology, formation

University of Catania: medical physics

University of Florence: medical physics

University of Turin: interface beam-patient, TPS

Polytechnic of Milan: patient positioning, radioprotection, authorisations

European Institute of Oncology: medical activities, authorisations

San Matteo Foundation: medical activities, logistics

Town of Pavia: land and authorisations

Province of Pavia: logistics and authorisation

International corresponding institutions

CERN (Geneva): technical issues, PIMMS heritage

GSI (Darmstadt): linac and special components

LPSC (Grenoble): optics, betatron, low-level RF, control system

Med-Austron (Vienna): technical collaboration for MA centre

Roffo Institute (Buenos Aires): medical activities

NIRS (Chiba): medical activities, radiobiology, formation

Conclusions

CNAO may be ready for the clinical study on the early of next year (2011).

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Status of the ETOILE Centre at the End of 2010

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Abstract

Since its last presentation during the NIRS – ETOILE symposium of March 2009, the ETOILE project went through a series of steps that have altered its general organization but has consolidated its future. Many programmes have been pushed forward altogether, as previously announced. First, the tendering process developed as a tentative public-private partnership reached an unsuccessful end. This decision was made in full agreement with the administrative authorities. Second, the solution to include in the project a high-performance research facility capable of prolonging the present research programmes, as well as to attract and host visiting research teams was greatly improved. A dual-purpose centre, with mutualisation of the costs and resources, is now being proposed: the ETOILE Hadrontherapy Care Centre and the ETOILE Platform for Research and Development in Hadrontherapy (PRDH-ETOILE). This project was warmly welcomed by research and teaching institutions, and industrials. Third, the governmental health authorities gained full and satisfactory information through a long process of evaluation and negotiation and issued, in October 2010, a set of recommendations to go ahead with this solution, among which: i) the "green light", of course, to launch a new tendering process with a public body project ownership; ii) the engagement of the State to create a specific national public health centre to host the care activities and to allow its funding through the health insurance system; iii) the latter clause being granted provided the research part is auto-funded; iv) the agreement to send an increasing number of patients to already existing carbon ion care centres abroad, in order to constitute a cohort of hadrontherapy cases in France, to begin treatments and studies, and later on training for the opening of the Centre. Thus, 2011 should be a very busy, and hopefully successful, year for ETOILE.

Introduction

The French hadrontherapy project was launched in 1997 at University Claude Bernard Lyon 1 (UCBL). The project became the ETOILE Centre in 2008 (www.centre-etoile.org), the construction of which was assigned to the GCS-ETOILE, a public joint structure comprising three university hospitals and the two public anti-cancer centres of the Rhône-Alpes Region. The first tendering process was a tentative public-private partnership procedure set up by the GCS from 2008 to 2010, which eventually proved to be unsuccessful.

Since 2000, the scientific programme for ETOILE has been structured into a multidisciplinary research cluster in hadrontherapy (PRRH, Programme Régional de Recherche en Hadronthérapie), within the UCBL, and involving about sixty researchers belonging to approved teams. This cluster is the research activity of the ETOILE Project, actively participating to various international programmes such as the European FP7 ULICE, ENVISION, PARTNER projects carried by ENLIGHT++. This cluster will provide the core of the ETOILE

Platform for Research and Development in Hadrontherapy (the PRDH-ETOILE) that will be part of the future ETOILE Centre itself. The French National Cancer Institute (INCa) recommended in its 2005 report to the Ministers of Health and Research the extension of this effort to a National Hadrontherapy Research Programme (PNRH). In 2004 the CNRS had launched its GDR-2917 MI2B (Modelling and instrumentation for Biomedical Imaging) research group, encompassing about a dozen of laboratories. This research group evolved at the end of 2009 into the "Instrumentation and nuclear methods in the fight against cancer" project. Together with the Regional Programme for Research in Hadrontherapy, this consortium of CNRS laboratories represent the two main scientific and medical pillars of such a national programme, of which the ETOILE Centre is expected to constitute the main medical and scientific contributors, with its skills in both domains, its therapeutic capacity and its fast growing patient cohort associated with its research platform.

This national programme also has the responsibility to coordinate the two leading French projects: on the one hand, the ARCHADE association's project (www.archade.fr) for a Centre dedicated to upstream research on nuclear fragmentation and R&D on cyclotron accelerator technologies, to be completed in Caen in the coming years; on the other hand the PRDH-ETOILE which, for its part, has the objective of allowing patients of the national hadrontherapy treatment centre to benefit from the research conducted over the past 10 years in Rhône-Alpes by developing R&D designed to optimise treatment.

During 2010 these different aspects of the ETOILE Project underwent important evolutions, as detailed below.

The Tendering process and the construction previsions

Figure 1: Location of the future ETOILE Centre. The ground has been bought by the GCS-ETOILE in December 2009.

The first tendering process started in February 2008 as an attempt to set up a Private-Public Partnership (PPP) which had been recommended in 2007 by the French Administration in the hope to allow the completion of the project without augmenting the national public debt. This process was described in detail in a dedicated paper at the 2009 NIRS-ETOILE's Symposium in Lyon.

The final phase of the PPP process was accompanied by one proposal, including an innovative and never yet built accelerator, which was therefore sensed as a "risk" by the main financing institutions in the answering industrial consortium. Not only did this risk considerably raise the overall cost of the process, but as implied by the French law system, most of it was put on the public person's charge, and hence the proposal was not viable. After a report to the Administration, this unique final proposal was rejected.

Immediately following this drawback, a new tendering process was launched by the GCS in November 2010, with ownership of the project to the public body, and the acceptance clause that the offer should not include a prototype. It is now projected that the contract will be signed before the end of 2011, the construction will start in 2013, and the first patients of the ETOILE Centre will be treated in 2016.

Many things will have to be done meanwhile

1. The consolidation and the development of the ETOILE Platform for R&D in hadrontherapy

The ETOILE Centre will be the only establishment in France to offer carbon ion therapy. It will allow approximately 250 additional people a year to be cured per 1,000 patients treated (i.e. +20 to +30% compared to conventional treatment for this type of pathology). The highest-priority indications have been defined and represent approximately 1,200 cases per year in France. The 2003 and 2009 French Cancer Plans mention the advantage of this therapeutic approach.

However, numerous biological, medical, economic and technological questions remain to be addressed, in order to optimise current solutions and overcome the still persisting technological obstacles. These include as many opportunities for technological development and applications based on particle physics and expertise in high-level nuclear acceleration technologies. This know-how, a world away from medicine, opens up a new industrial field in health technology, biotechnology and medical imaging at the margins of the traditional medical industry. As this technology is emerging, it therefore represents an open opportunity for industrial development based on finalised research developed as close as possible to the treatment centres.

In the current development phase of this technology quite exclusively in Europe and Asia, France needs to strengthen its position by creating an R&D platform on a national scale, attractive to public and industrial, national and international research teams, in particular by responding to the lack of access to ion beams and clinical data (overseas treatment centres rarely being open to research).

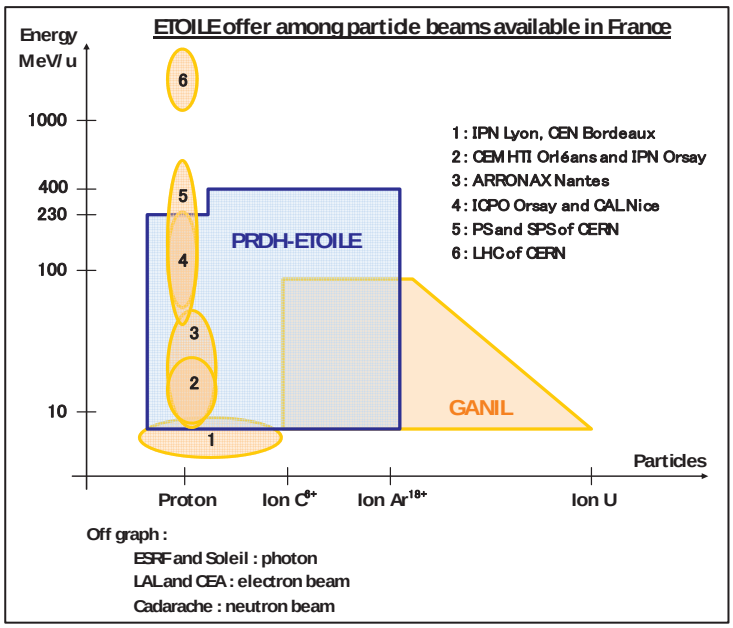


Figure 2 shows the comparative offers of different institutions in France as beam resources for research. The future ETOILE offer appears rather large and attractive within this frame.

Figure 2: Distribution according to particles and energies in the ion beam offer in France.

The ETOILE Centre will therefore have dual activities managed in the same institution (refer also to Figure 5):
1) The only ultra-specialist treatment centre in France offering carbon ion treatment with a clinical research objective, networked with the other French protontherapy centres (Nice and Orsay) and European carbontherapy

centres (Germany, Italy, Austria) as a member of the European programme ULICE (Union of Light Ion Centres in Europe) .

2) A Research and Development Centre in Hadrontherapy at an international level developing three major R&D topics based on clinical needs, in partnership with French public research institutions (EPST and EPIC in French) working in the field. The centre will have the capacity to attract and receive external public and industrial, national and international research teams, in particular in the response it offers to the lack of access to ion beams.

This research activity will rely on a very complete technical facility, including a research room equipped with a dedicated hadron beam and specific instrumentation, a radiobiology laboratory, an animal house, clinical databases and a shared imaging facility, located in the same building as the treatment centre. A dedicated team in close connection with the in-house researchers will operate the facility. This facility will constitute the ETOILE Hadrontherapy R&D Platform (PRDH-ETOILE).

The PRDH-ETOILE will be in fact an original structure having the advantage to share building, equipment, maintenance, manpower and running expenses with the care centre that will take over most of these expenses. Hence, the residual — albeit "real" — cost of the platform will be rather low for such a facility. Figure 3 shows the distribution of the financial burden of the ETOILE Centre. Actually, most of the investment cost of the Platform will be solicited in the frame of the call for project of the "investment for the future" launched this year by the French government to sustain economical development in France. The answer to this procedure is expected at the beginning of 2011.

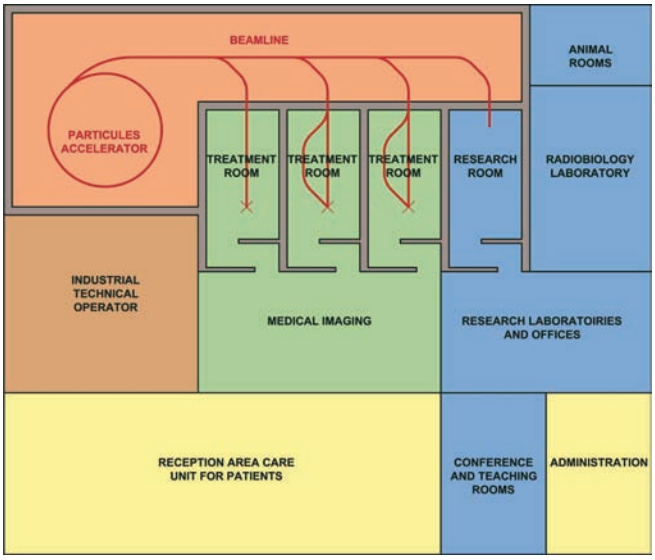


Figure 3: Distribution and sharing proportion of the ETOILE surface between the use for treatment and for research.

In yellow: 100% treatment

In blue: 100% research

In green: 90% treatment, 10% research

In orange and brown: 80% treatment, 20% research

2. The beginning of an organized pathway of hadrontherapy for French patients treated abroad in the frame of the ULICE programme

For economical reasons, the ramp-up of the recruitment of the ETOILE Centre after its opening will have to be very fast, combining protons and carbon ions treatments as shown on Figure 4 below. To succeed this, it is necessary to manage the recruitment of patients and the training of the medical and technical teams *before* the opening of the centre, at the same time.

OMéRRIC (*Medical Organization of the Recruitment for Carbon Ions Radiotherapy*), a specific network organization at the national scale, is being set up by the GCS-ETOILE. This organization has developed different tools for the recruitment, the addressing and the follow up of patients. After patient cases will have been identified by local Multidisciplinary Tumor Boards anywhere in France, the medical records will be submitted to the

ETOILE Technical Committee that will consider whether they are suitable for hadrontherapy or not. Then, provided the patient is willing to do so, its medical record will be submitted to the medical board of one of the Carbon ion centers in Europe (only Heidelberg presently). This scheme should, as much as possible, be set up in the frame of the European FP7 ULICE programme.

The French Ministry of Health requested the GCS-ETOILE to organize this recruitment in the frame of a medical assessment programme for this cohort of patients.

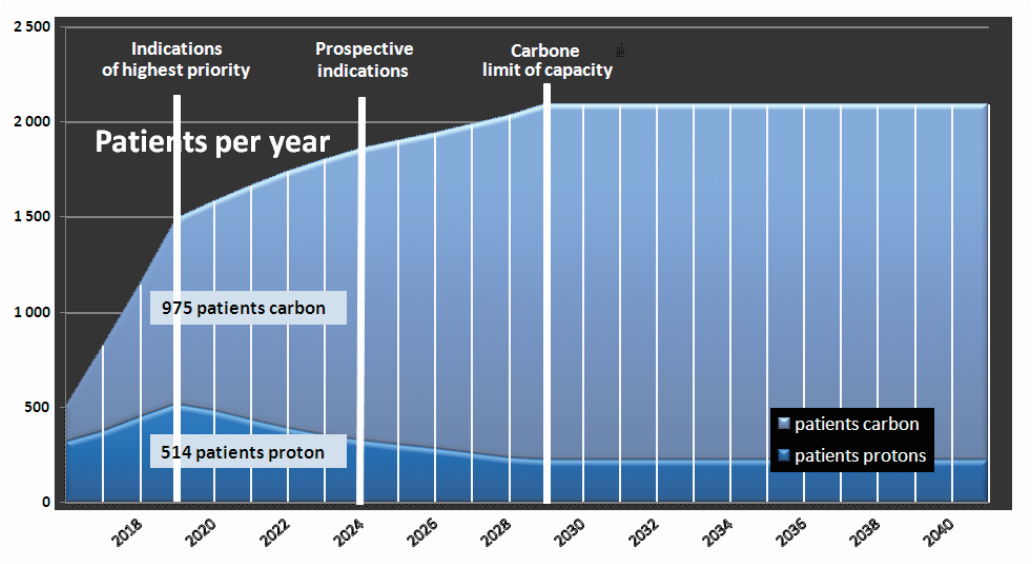


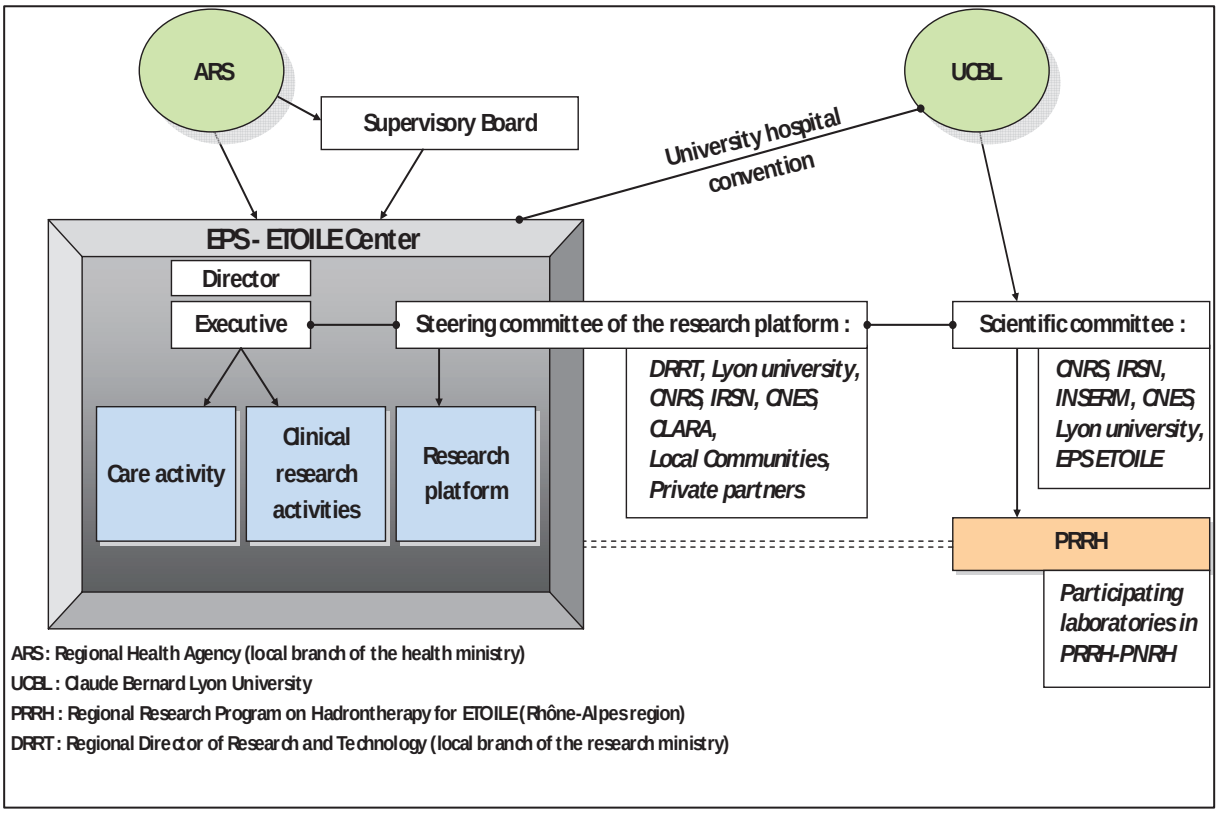
Figure 4: The prospective activity of the ETOILE Centre.

3. The launching of a clinical research programme based on the initial cohort of patients

The GCS-ETOILE has proposed, within the French programme for clinical research (PHRC), an annual national call for projects, *to start* the development of a prospective comparison of carbon ion therapy and advanced photontherapy techniques, or protontherapy, for a small set of indications with the highest priority. The main objective is a prospective comparative evaluation of disease-free survival of carbon ions therapy and alternative radiotherapy modalities for localized unresectable (or R2) radioresistant cancers: sarcoma, chordoma, adenoid cystic carcinoma. The secondary objectives will be, among other things, to assess overall survival, local relapse-free survival, toxicity profiles for the various treatments. For each targeted disease, two groups of patients — the first one with carbon therapy and the second one with alternative radiotherapy modalities — will be constituted with an 1:3 expected ratio. The two groups will have the same follow-up modality (tumor outcome data; acute and late and late effects; analysis of recurrence and second line treatments) to allow prospective matching comparative studies.

The registration and the prospective collection of information will be organized by the GCS-ETOILE through its OMéRRIC network. This initial study will require 160 patients including 40 cases treated with carbon ions (for the two first years recruitment). A 20 to 25% absolute difference in favour of carbontherapy is expected, that would require around 50 patients treated with carbon ions for each pathology sub-group selected in that study. Therefore, as a whole, the expected recruitment in that specific study is 60 patients for the first year (including 15 treated with carbon ions) and 100 patients for the second year (including 25 treated with carbon ions). The cohort will be extended with an expectation of 200 patients (50 carbontherapy) per year thereafter that will allow to gather, over a 5-year recruitment period, a cohort of 760 patients including 190 treated with carbon ions, as required for a final and relevant statistical comparative analysis.

However, the methodology described in that project will be applied until the opening of the ETOILE Centre, that is for a total of 5 to 6 years. The follow-up of the patients will be planned for 5 to up to 15 years, according to the pathologies.



Figures 5: Organisation of the internal governance of the future Public Care Establishment (EPS)-ETOILE and the PRDH-ETOILE.

Conclusion

In spite of a rather slow progression pace, the ETOILE Project is still in good tracks whatever the difficulties to overcome. One of the reasons for the delay in the construction of the centre is the very cautious decision process of the Health Administration. Actually, the fast progresses in medical sciences with the very fast turnover of medical techniques over the recent decades make it really hard for a national organization to bet on a 25 or 30 years investment regarding a medical facility devoted to a unique medical technology. The growing visibility of ETOILE in France and the inter/national position of its scientific programme, that managed to sustain active and valuable research for years, have strongly contributed to the decision of the Health Administration to support the project for the national medical and research centre under the condition that its scientific part (*i.e.* the R&D platform) be funded completely apart of the health care part; in other words, that the R&D platform is favourably assessed through an international jury, as commissioned by the National Loan scheme (Investissements d'Avenir) to which it has subscribed for specific research funding .

Particle Therapy Center Marburg
A Combined Proton – Carbon Ion Treatment Facility
Status Report

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Abstract

The RHÖN-KLINIKUM AG and its subsidiary the University Hospital Giessen and Marburg GmbH build a combined proton and ion beam therapy facility at the University Hospital Campus in Marburg. The facility is based on a synchrotron accelerator that feeds four treatment rooms. It is intended to treat tumor indications of the whole body. The treatment of patients is supposed to start in the second half of 2011. Current Status: The building for the facility is completed. The accelerator optimization and the parameter tuning for the beam library is ongoing. First Beam Scanning has been performed in treatment rooms one and two.

Fig 1. Particle Therapy Center Marburg

Project Overview

RHÖN-KLINIKUM AG (RKA) is the largest private German hospital company with 54 hospitals at 43 sites having approximately 17.000 beds in total. Intending to offer a highly effective radiotherapy for its patients in future, RKA has developed and designed a combined proton and ion beam therapy facility (=particle therapy facility).

RKA installs the Particle Therapy Center (PTC) at the University Hospital Marburg, one of two sites of the University Hospital Gießen and Marburg GmbH (UKGM), a subsidiary of RKA. The facility consists out of four treatment rooms with a fixed beam lines.

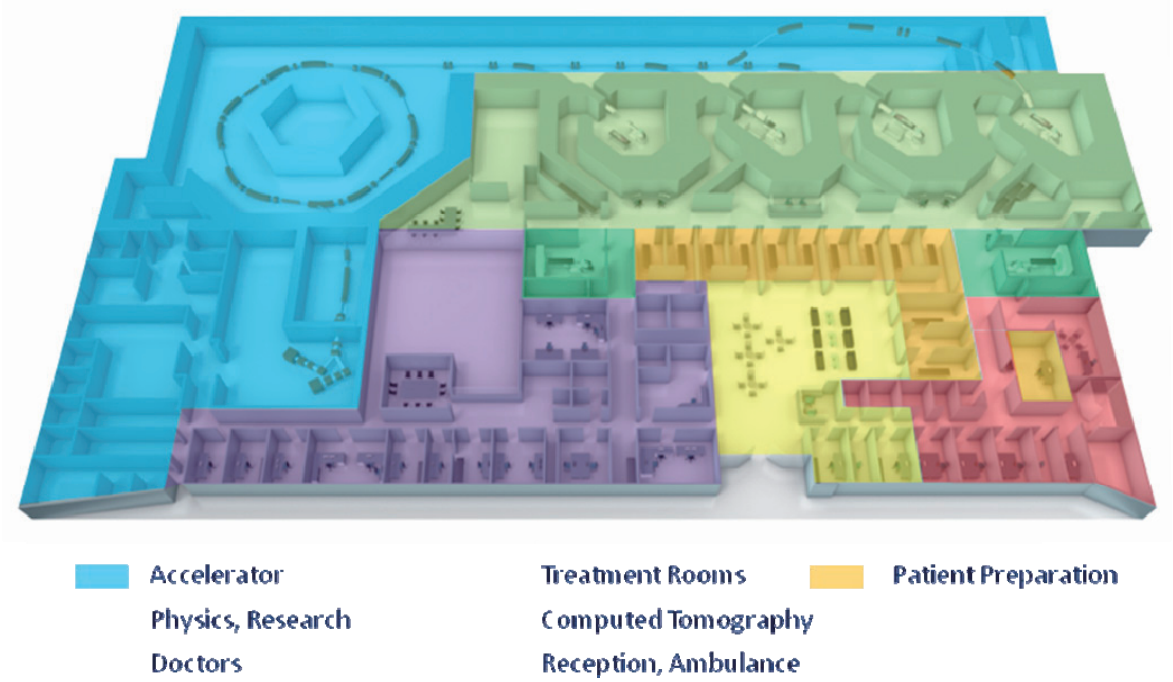

Fig 2. Layout of the facility (ground floor)

The layout of the facility has been carefully designed for an optimal patient care keeping the inconvenient fixation time short and to yield a smooth patient flow (2000-2500 per year). Therefore spacious patient areas in a minimum distance between treatment rooms and preparation rooms will be provided.

The project has been started in summer 2007, clinical operation is planned to start in the second half of 2011.

Clinical operation will be performed by UKGM. The PTC Marburg will be part of the Clinic for Radiation Therapy. It will use diagnostical infrastructure, research environment and oncological competence of UKGM in terms of a comprehensive cancer treatment approach.

Layout

The PTC facility has a clear structured workflow optimized layout (see Fig. 2). All treatment relevant functions are placed on one floor level. The patient preparation area is located right in front of the treatment rooms. Ambulance, medical area and medical physics are arranged in direct connection to the patient area.

1. Accelarator

PTC Marburg uses an ion source – LINAC – synchrotron accelearator layout to provide two ion species for treatment. The accelerator is designed to accelerate ions up to 430 MeV/u.

Design parameters are:

Protons 50 – 220 MeV , 2E10 per spill
Carbons 85 – 430 MeV/u, 3E8 per spill

2. Treatment Rooms

The facility consists out of four treatment rooms where three are equipped with a fixed horizontal beam line and one with an oblique (45°) fixed beam-line.

Each treatment room is equipped with a beam application system providing Raster Scanning with active energy variation by synchrotron in maximum treatment field size of 20 x 20 cm^2.

For patient positioning robotics based treatment tables are installed in each treatment room. This gives a maximum of positioning flexibility in combination with very high precision and allows tilt and roll of the table up to +/- 15° for beam angle variation.

Fig. 3: PTC Marburg – Treatment Room (Foto: Siemens)

A robotics based X-Ray-System is used for position verification and image guided radiotherapy. The Cone Beam CT ability of this system will allow high contrast imaging for all tumor indications.

Current Status

Construction of the facility has been finished May 2009. Installation of the accelerator system including support systems has been completed end of 2009. All treatment rooms are completely equipped since summer 2010.

First Beam Scanning has been performed in treatment rooms one and two in August 2010.

Currently the accelerator optimization and the parameter tuning for the beam library, system and IT integration are ongoing.

The treatment of patients is supposed to start in the second half of 2011.

SAGA-HIMAT (Heavy Ion Medical Accelerator in Tosu) —The First Japanese Heavy Ion Therapy Facility Constructed and Operated by Public-Private Partnership

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Due to physical and radiobiological advantage, the potential of heavy ion beams for cancer therapy has been recognized for a long time, and clinical trials at HIMAC (Heavy Ion Medical Accelerator in Chiba) have shown excellent results. Following the success of HIMAC, several facilities have begun treatment or are now being constructed worldwide. In Japan, the Hyogo Ion Beam Medical Center has treated patients for more than seven years and Gunma University has also begun to treat patients since March 2010. However, all three Japanese facilities including HIMAC have been constructed and operated by the public sector, because construction and operation of a heavy ion therapy facility requires a huge budget that is difficult for private hospital to afford. In order to allow more cancer patients benefit from the use of heavy ion beams, we started the project to construct a heavy ion therapy facility by public-private partnership.

To construct the facility, named SAGA HIMAT (heavy ion medical accelerator in Tosu), A special purpose company (SPC) and a foundation were established to accept investment and donation from private companies, respectively (Fig. 1). Local governments decided to provide the land and a part of construction cost. The SPC and foundation will jointly construct and operate the facility.

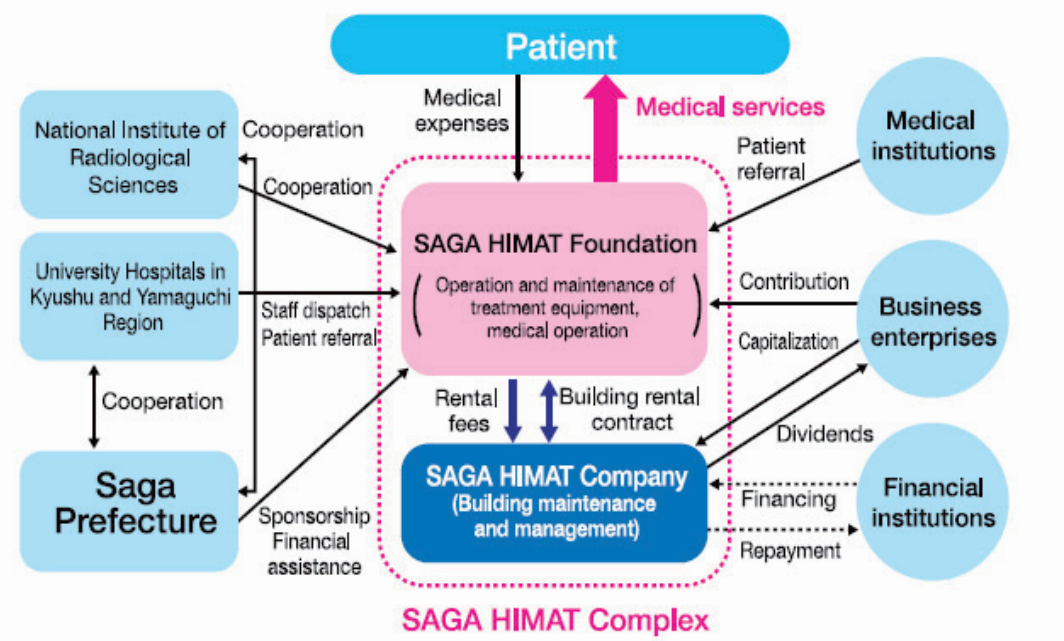

Fig. 1 Outline of the SAGA HIMAT Project

The construction site is located at the city of Tosu, Saga prefecture. The city is near to Fukuoka, the largest city in Kyushu-island and is the cross-point of railroad and highway networks (Fig. 2). Moreover, the facility will be constructed just adjacent to Shin-Tosu station of Kyushu Shinkansen (bullet train). The convenient access to the facility will be beneficial to not only residents in Kyushu-island and also those in south west part of Japan other than Kyushu-island. The SAGA HIMAT will begin treating patients in 2013.

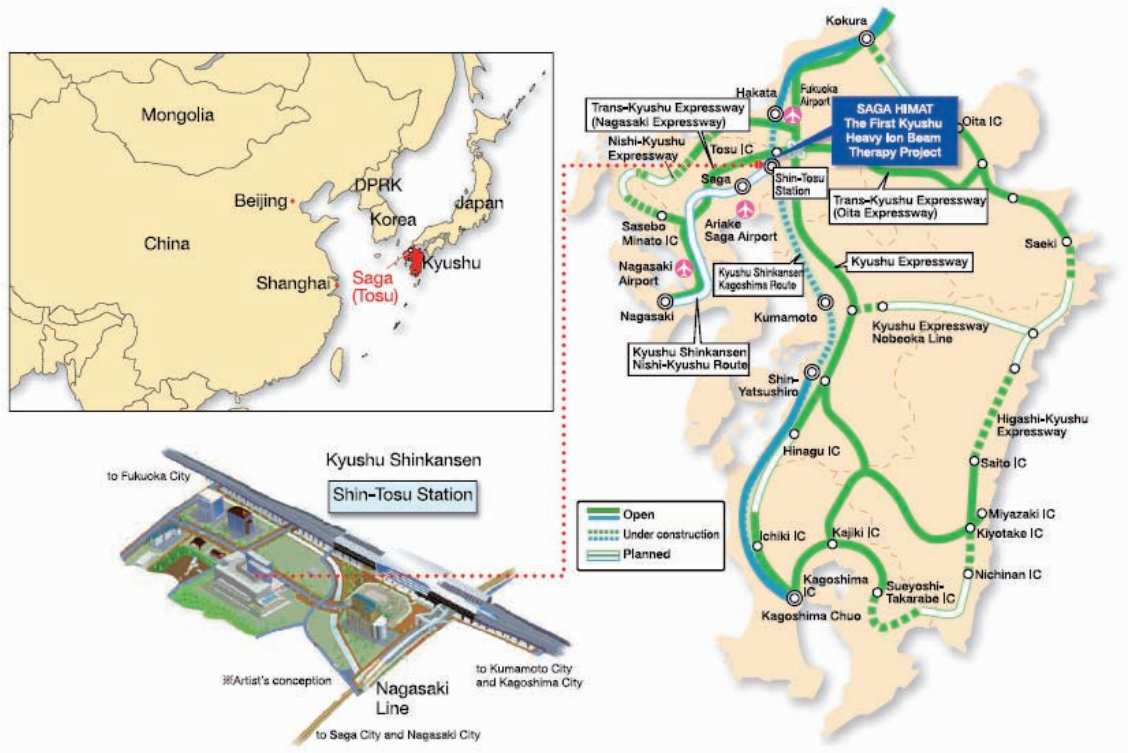

Fig. 2 Planned construction site for the SAGA HIMAT.

Current Status of MedAustron

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Abstract

The ion beam cancer treatment and research centre MedAustron in Wiener Neustadt, Austria is designed to be a dual beam centre where proton and carbon ion beam therapy can be compared under identical technical conditions. A substantial task of MedAustron will be therefore, apart from the treatment of recommended indications, also the scientific consolidation of not yet statistically validated treatment results. The company EBG MedAustron Ltd. has the overall responsibility for the construction and operation of the MedAustron cancer treatment and research centre. Within this framework, the planning and realisation of the particle accelerator facility, based on a synchrotron for the delivery of protons and carbon ions, is being made in cooperation with the European Organisation for Nuclear Research (CERN), the world's largest institute for particle physics. In phase I, the center will encompass three treatment rooms (one horizontal fixed beam, one horizontal and vertical fixed beam, one proton gantry) and one room for non-clinical research. Later, in phase II, a fourth treatment room will be added, possibly equipped with an ion gantry, depending on the experience of existing facilities and further technological development. The first patient treatment is scheduled in 2015. Once the centre is in full operation, it will be possible to treat 1,200 patients per year.

Overview

The Federal State of Lower Austria will build and operate the cancer treatment and research centre MedAustron through the EGB MedAustron Ltd. with a 100% controlling interest. The EGB MedAustron Ltd. has the overall responsibility for the construction and operation of the facility. The planning and realisation of the particle accelerator facility is performed within a co-operation with the European Organisation for Nuclear Research (CERN); the planning and follow-up of the site infrastructure are contracted to a consortium of Austrian architects. The Federal State of Lower Austria will assume the liability for 120 million € and will contribute to the construction costs for non-clinical research with 3.7 million €. The City of Wiener Neustadt covers 1.9 million € of the construction costs and provides the site (3.2 ha).

The company PEG MedAustron Ltd., owned jointly by the Republic of Austria, the County of Lower Austria and the City of Wiener Neustadt, is in charge of the start-up financing of the non-clinical research installations in the MedAustron project. The Republic of Austria provides 41.0 million € for the construction and 5.5 million € annually for operating costs and for non-clinical research. PEG MedAustron will provide the infrastructure for non-clinical research along with a comprehensive support service for the researchers coming from national and international research institutes and from industrial companies to use the proton and carbon ion beams.

Epidemiological evaluation

Precise data were required to most accurately define the number of potential patients for ion beam therapy in Austria [1]. In order to answer this question a so-called “epidemiological survey” was performed; for this study, disease and treatment related data on all patients receiving conventional curative or palliative radiotherapy at all twelve operational Austrian radiotherapy facilities were collected during a period of three months. Epidemiological cancer incidence data (Statistic Austria 1999) were correlated with the number of patients receiving conventional radiotherapy. Based on published clinical and experimental results on proton and carbon ion therapy, a calculation of patients’ subgroups suitable for ion beam therapy was performed at five European university hospitals involved in the HICAT, CNAO, ETOILE and MedAustron project. Using the mean values of the university specific percentages per tumour site, the number of potential patients was estimated. The results were as follows: in Austria a total of 3783 patients started conventional radiotherapy (photons/electrons) during the study period of three months resulting in an approximated number of 15 132 patients per year. Using the above described method, the number of potential patients for ion beam therapy was estimated to 2044 per year, representing 5.6% of all newly diagnosed cancer patients and 13.5% of all irradiated cancer patients in Austria.

As conclusion from this study, MedAustron is designed to treat 1200 patients per year in its full operational phase.

Project Management organisation

1. Sub-projects

The project is organised in form of sub-projects that are coordinated by the overall project management team. The sub projects are:

- medical project (medical equipment, medical physics and research equipment);
- accelerator project (accelerator complex and technical infrastructure for accelerator)
- civil engineering project (civil engineering, general technical infrastructure);
- non-clinical project (non-clinical technical and other requirements, equipment aspects).

2. Timetable for implementation of the project

On a large scale, the project time schedule is driven by the project phases of

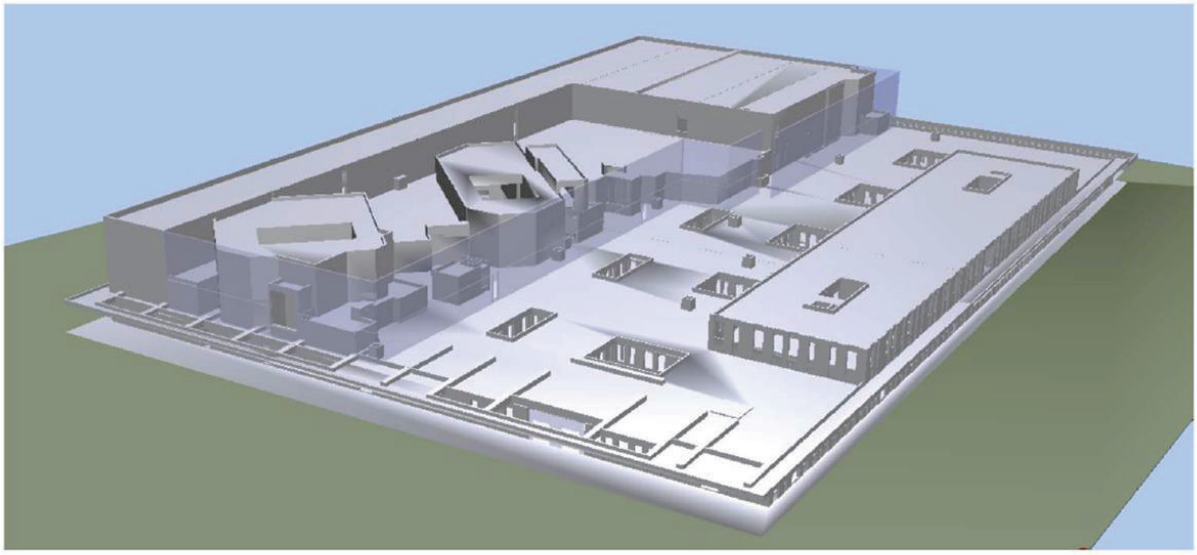
- conceptual design of the civil engineering and the accelerator,
- environmental impact assessment, building construction,
- accelerator installation, commissioning (without patient)
- certification for patient treatment.

The civil engineering pre-planning started in May 2008 and I was based on user specifications (medical treatment and non-clinical research requirements) and on the requirements from the accelerator complex to be integrated in the facility. In parallel the documents required for the mandatory Environmental Impact Assessment (EIA) were prepared and submitted to the authorities in autumn 2009. The authorities’ approval will be received in December 2010. After a final planning phase, the ground-breaking and the start of building construction is foreseen for spring 2011. In 2012 the technical building will be ready to start installation of technical infrastructure and the first accelerator components. The first patient treatment will only take place after completion of commissioning and certification of the facility by the authorities and is scheduled in 2015.

Technical description of the project

1. Building

The project will be realised within the industrial zone “Civitas Nova” located in the northern periphery of Wiener Neustadt. The building will be characterised by a clear zoning of the various functional parts of the project.



The ground floor will house the medical part, the research part and the accelerator part. The basement will accommodate the technical infrastructure for the building services and for the accelerator. The administrative area will be situated in the upper floor.

The specific parts will be arranged to a compact layout, which minimises the surface areas and as such enables a cost-effective construction and an economic operation of the building. Large size glazing will establish a visual link between inside and outside areas. Green patios will create an agreeable atmosphere for patients and personnel and will enable the illumination of internal rooms with natural daylight.

The utilisation of natural daylight together with intelligent sun protection devices will minimise the energy consumption for electric lighting and air-conditioning.

2. Technical equipment

2. 1 Accelerator complex

The MedAustron accelerator complex consists of an injector, a synchrotron as main accelerator and the extraction line, that brings the beam towards the treatment rooms. The accelerator complex is designed to allow fully active beam delivery which is presently the most advanced technique in the field of hadron therapy. The complex will cycle with a typical repetition rate of 0.5 Hz and beam energy, size and intensity can be changed on a cycle-to-cycle basis. A change of the ion type, i. e. protons or carbon ions will also be possible on the sub-minute level. The design of the accelerator complex is based on machines that already exist or which are in the process of being built and also takes into account experience from running facilities. Collaborations for the realization of the MedAustron accelerator complex have been established with the European Organisation for Nuclear Research (CERN) and the Italian CNAO hadron therapy centre.

2.2 Injector

The injector will comprise three ion sources with the possibility of adding a fourth source. Two sources (protons and carbon ions) are the standard configuration for medical treatment, the third source serves as spare and the alternative fourth source can be used for research with a different ion type. The sources are connected by the low-energy beam transport that brings the beam from the active source to the radio-frequency quadrupole that serves as pre-injector for the drift tube linac. The drift tube linac (IH structure) will accelerate the beam to 7MeV per nucleon which is the injection energy of the synchrotron.

2.3 Synchrotron

The synchrotron is based on the CERN Proton Ion Medical Machine Study (PIMMS) [2] and was further developed into a technical design by the Italian CNAO group. The synchrotron will use the so-called “slow resonant extraction” method to provide the beams for treatment. The energy range is 60MeV to 250MeV for protons and 120MeV per nucleon to 400MeV per nucleon for carbon ions.

2.4 Extraction line

The extraction lines are based on a modular concept that was developed within the PIMMS study at CERN [3]. The beam size is controlled in the common part of the line and the beam is then passed onto the different treatment rooms by similar beam line modules with special optical transport properties. This concept is expected to ease operation because of similar beam optics settings.

3. Medical equipment

3.1 Beam-lines at MedAustron

Phase I

To ensure optimal ion treatment at the MedAustron facility, the following equipment will be available from the beginning on:

- one horizontal beam-line for protons and carbon ions;
- one horizontal and vertical beam-line for protons and carbon ions;
- one proton gantry.

Phase II

In the medium/long-term a fourth treatment room will be added, possibly equipped with an ion gantry, depending on the experience of existing facilities and further technological development.

3.2 Mode of beam delivery at MedAustron

Beam scanning will be implemented on all beam-lines. The reasons are greater flexibility in treatment planning in terms of treatment plan optimisation and superior dose distributions allowing a significantly reduced neutron dose at the patient level.

3.2 Medical imaging at MedAustron

Many research activities in radiation oncology focus on approaches to modify the treatment during its course, possibly several times, in order to account for time variable effects, i. e. weight loss, changes in organ filling, changes in tumour shape due to response. All these anatomic and biologic variations can be determined using the following imaging equipment: CT, MRI, ultra-sound etc. These adaptive and image guided therapy approaches will directly influence combination therapy strategies. The MedAustron facility will be equipped with all those imaging tools to meet the future requirements for adaptive radiotherapy.

Co-operations

Co-operations with other centres in Europe, built up during the EU-project “European Network for Light ion Therapy (ENLIGHT)” will be expanded. European projects like the ongoing project “Union of Light Ions Centres in Europe (ULICE)” will strengthen the co-operations to other similar institutions. This will result in a

strong interconnection between the European ion centres, however also co-operations with centres beyond the European region will be strongly encouraged by MedAustron.

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NRoCK - Status Report

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Summary of paper

As a center of competence for malignant tumors at the Medical University Center Schleswig-Holstein (UK S-H), NRoCK will offer new treatments for cancer therapy beginning in 2012. After a two year preparation phase, actual construction of the building began in July 2008.

NRoCK will be among the most innovative centers worldwide for cancer treatments with UK S-H offering the entire spectrum of all modern radiation techniques, as well as systemic therapy and full imaging diagnostics under one roof. This ensures an optimal clinical process from initial diagnosis to therapy and after-care. For particle therapy, an especially tissue-sparing and precise form of treatment will be available.

In close cooperation with partner institutions from Northern Germany and the Baltic, patients will be receiving specialized therapy sparing to the patient. At the same time, experts at the NRoCK will continue to drive research in the area of particle therapy and train expert personnel.

The decision in Kiel calls for building a combined system that allows the use of other particle types in addition to protons. This provides the prerequisites for ongoing scientific research focusing on efficient tumor treatment with particles.

In view of expenditures amounting to 250 million Euros, NRoCK is one of the largest projects within the German healthcare system which will be realized as a public-private partnership. The project partners are UK S-H and a consortium of Siemens AG, Bilfinger Berger, and HSG Zander. The consortium is charged with the construction and operation of the center.

The contract between the bidding consortium and the UK S-H covers planning, construction, financing as well as technical operation including maintenance for the particle therapy system in a public-private partnership over a period of 25 years.

Introduction of Shanghai Particle Therapy Center

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Cancer is number 2 killer after cardiovascular diseases in Shanghai. The project of Shanghai Particle Therapy Center (SPTC) started in 1998, but was failed because of the huge budget until 2007, when Shanghai Municipal Government decided to invest this project.

SPTC will be a non-profit hospital affiliated to Fudan University Shanghai Cancer Center (FUSCC). FUSCC is the oldest cancer center in China, which was founded in 1931 by Kingdom of Belgium and the original name was “Sino-Belgium Radium Institute (SBRI)”. Late SBRI became one of the teaching hospitals of Shanghai Medical School, and then one of the affiliated hospitals to Fudan University, which is one of the leading universities in China. Now FUSCC is a comprehensive cancer center with 12 clinical departments, including surgery, radiation oncology, medical oncology, traditional Chinese medicine, etc. The department of radiation oncology is facilitated with 8 linear accelerators, and modern radiation therapy technology has been established there, including 3-dimensional conformal radiation therapy, intensity modulated radiation therapy, image guided radiation therapy, dose guided radiation therapy, and moving target control techniques (active breath coordinator, respiratory gating, etc). 4600 patients were treated by irradiation in 2009 with over 500 patients daily.

SPTC locates in suburban area of Shanghai, and will have 220 in-patient beds and provide irradiation and chemotherapy to cancer patients at that location. However, multidisciplinary care will be carried out for cancer patient management, and when patients need surgery they will be referred back to FUSCC main campus.

SPTC will provide patients irradiation with photon, proton and carbon beams. The proton and carbon will be produced by Siemens synchrotron and it will be associated with the most advance irradiation technology: pencil beam scanning, robotic arm for patient set-up and image guided irradiation therapy. There will be four treatment rooms with a horizontal beam, a combination of horizontal and perpendicular beams and another combination of horizontal and 45 degree beams, respectively for 3 rooms and the last one for research in SPTC. The photon irradiation will also be provided in that hospital, mainly for superficial lesions, e.g., metastatic neck nodes from nasopharyngeal carcinoma, or for lesions, which are very closed to organs at risk (OAR) or inside of OAR. The linear accelerator will be ARTIST from Seimens with CT on rail for adaptive radiation therapy. A radiobiology lab in FUSCC will be shifted to the studies of heavy ion.

The civil construction of SPTC was started in August of 2009, and will be completed by the end of 2010. The installation of facilities will be begun at the middle of 2011. The photon therapy will be scheduled to treat patients by the end of 2011. The first beam will be available by the middle of 2012.

The San Francisco Bay Area Particle Accelerator Research Center (SPARC): a Collaborative Effort between Stanford/SLAC & LBNL/UCSF

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Disclosures:
None

Disclaimer:
The thoughts and opinions in this paper are those of the author and not meant to imply binding commitments on the part of other individuals or institutions mentioned. This manuscript represents a status report of the plans for building a Particle Facility in the San Francisco Bay area as understood by the author when it was prepared and subject to change.

Abstract:
Phase I Trials for treatment of cancer patients with charged particles at the UC Lawrence Berkeley National Laboratory (LBNL) began in 1975 with helium ions. In 1977 the first carbon ion patient was treated. Unfortunately after 17 years and approximately 1000 patients treated this facility was closed in 1992. In the mean time, following the lead of investigators from LBNL several other facilities sprung up in Japan, Germany and other sites worldwide. Herein we summarize our ongoing efforts to reestablish a Particle Therapy Facility in the San Francisco Bay Area as a joint venture between two large physics research institutions: LBNL, the Stanford Linear Accelerator Center (SLAC), and two major academic institutions: Stanford University Medical Center (SUMC) and the University of California San Francisco (UCSF). This joint effort grew out of what were initially independent efforts between UCSF and LBNL and between SUMC and SLAC. Although a formal name for this endeavor has not been adopted for the sake of this report I will use the term San Francisco Bay Area Particle Accelerator Research Center or SPARC (pronounced "spark") when describing this entity. Much of the detailed work concerned the design and construction of the facility envisioned was performed by a Task Force from SLAC and SUMC, while ongoing clinical and radiobiological collaborations addressing patients previously treated at LBNL continues to be lead by investigators from LBNL and UCSF.

Introduction:
The use of charged particles for medical radiotherapy was first suggested in 1946 by physicist Robert Wilson [1]. He also hypothesized that carbon ions might be superior to proton beam radiotherapy. It was not until 1977, that the first carbon ion patient was treated on Phase I trials at the UC Lawrence Berkeley National Laboratory (LBNL) [2-5]. Unfortunately after 17 years and after more than 1000 were patients treated, this facility was closed in 1992. In the mean time following their lead several other facilities sprung up in Japan, Germany and other sites worldwide. Herein we summarize our ongoing efforts to reestablish a Particle Therapy Facility in the San Francisco Bay Area as a joint venture between LBNL, the Stanford Linear Accelerator Center (SLAC), Stanford University Medical Center (SUMC) and the University of California San Francisco (UCSF). Although a formal name for this endeavor has not been adopted for the sake of this report I will use the term San Francisco Bay Area Particle Accelerator Research Center or SPARC (pronounced "spark") when describing this entity. Much, of the detailed work concerning the design and construction and characteristics of this facility, was performed by the Task Force formed by SLAC and SUMC (from which this document draws heavily on). As a complement to this effort, ongoing clinical and radiobiological collaborations addressing patients previously treated at LBNL continues to be lead by investigators from LBNL and UCSF.

Background and the Strength of a Partnership:
Over the past 10 years particle radiation therapy has emerged worldwide as an accepted treatment option for the treatment of a variety of cancers [6]. It has been estimated that upwards of 50,000 cancer patients have benefited from this modality. World-wide more than 30 proton treatment facilities are either in operation or under

construction with the vast majority being in Japan and Europe but a rapidly growing number are being placed in the USA. At the current time, three facilities perform clinical treatment with carbon ions, two in Japan and one in Germany. In the next five years, as many as twenty-one additional centers providing proton therapy are expected to come online, while only six are projected to provide carbon therapy. With the exception of a small Proton Machine used exclusively for Ocular Melanoma, there are no particle radiation facilities in Northern California. More importantly we are aware of no carbon treatment facilities planned in the USA.

Of note, although most particle facilities are affiliated with medical schools, none of the existing major facilities in operation in the United States of America (USA), are associated with a major accelerator laboratory. Thus, research and development (R&D) efforts for addressing further development of particle technology are not likely to originate in the USA. In contrast, both the Heavy Ion Medical Accelerator in Chiba (HIMAC) in Japan, (part of the federally funded National Institute of Radiological Sciences), the Heidelberg Ion Treatment (HIT) Center, are both well positioned to lead innovative technology and R&D research with carbon ions. These two centers are the only facilities worldwide that combine accelerator laboratories with a medical school and a medical particle radiation treatment facility.

The two largest academic centers in the San Francisco Bay Area (Stanford and UCSF) with considerable expertise in radiotherapy and two large research Institutes with outstanding expertise in particle accelerator physics: Stanford Linear Accelerator Center and the UC Lawrence Berkeley National Laboratory (including heavy particle radiobiology in the latter), have formed a collaborative consortium in an attempt to bring medically oriented particle radiation therapy back to the Bay area and the USA. SPARC is envisioned to not only involve extensive technical R&D and medical effectiveness issues but to also address socioeconomic issues such as whether there are cost effective advantages to the use of varies forms of particle therapy compared to more conventional forms of external beam radiation such as Intensity Modulated Radiation (IMRT). Our major hypothesis is that by exploring this question now, we will save cost in the long run by either limiting the widespread proliferation of expensive but ineffective therapy, or develop a model for the appropriate cost effective application of this technology. Because of the strengths in population sciences, cost-effective studies, the medical application of radiation, radiobiology and accelerator physics we believe our four-institution consortium is uniquely positioned to test this hypothesis. We believe that the body of work resulting from this collaboration described below will yield an outcome far greater than expected from the sum of the parts.

The partnering of Stanford and SLAC with UCSF and LBNL represents an extraordinary opportunity. Representatives from these groups have been in active discussion for more than a year. These discussions have evolved to the point where the chairs of the Radiation Oncology Departments at UCSF and Stanford, the Deans of the Schools of Medicine, the Chief Executive Officers and chief operating officers and their strategic officers at SHC and UCSF, the accelerator department heads at SLAC and LBNL agree on all the major objectives and priorities. In particular, all the partners support a strong R&D component, the requirement for carbon beams and a broad-based treatment capability that includes a comprehensive pediatric component and a clear preference for a site on the peninsula somewhere between UCSF and Stanford with easy highway access.

Our immediate goals for SPARC are to:

1. Develop and implement a financially viable model to build a particle facility for conducting medical, biologic and physics R&D in collaboration with industry and other national and international centers.
2. Define the limitations of our current knowledge and recruit the expertise required to frame the key questions and define the most robust and cost-effective ways to answer them.
3. Build a multi-institutional alliance to conduct the Trials required.
4. Define the types of cancers that should most appropriately be managed with these modalities
5. Determine the relative effectiveness of Heavy Charged Particles compared to Protons and IMRT.
6. Develop strategies for creating an operational framework for minimizing the adverse impact of these technologies on the cost of Healthcare

Particle Beam Therapy is Effective but at What Cost?

Based on an extensive body of literature it is clear that particle beam therapy is highly effective [7-15]. What remains to be determined is whether other heavier charged particles are more effective and if so, how much more effective and whether it is cost effective enough to become an essential component of full-service cancer treatment [6, 16]. It is well known that particle beams have the potential to spare adjacent normal structures from unwanted radiation because of the lower doses of radiation scattered to surrounding normal tissues. IMRT with photon (X-ray) beams can also achieve quite conformal dose distributions, however large volumes of normal tissue are exposed to low doses of radiation, which is associated with an increased risk of second cancers.

Charged particles can deliver treatment with much lower exit doses and fewer beam angles and consequently lower doses to surrounding normal tissue.

The most obvious benefits to such proton beams are for treatment of tumors occurring in small children. For this group of patients there is little to no controversy. It is known that more than two-thirds of children who survive treatment for cancer with conventional therapy, experience, an increased subsequent risk of chronic health conditions 30 years later, with a cumulative incidence exceeding 40% for severe, disabling, or life-threatening conditions or death [17]. Another study suggests that the annual rate for secondary cancers after treatment for pediatric medulloblastoma (a common pediatric cancer) is 0.75% for X-rays and 0.05% for protons [18]. Unfortunately, due to economic pressures the vast majority of centers build in the USA have been financed based on the assumption that large numbers of patients coming to these centers would be treated for prostate cancer. In fact however, there are no data to justify the notion that either survival or quality of life would be enhanced with the adoption of Proton Beam Radiotherapy (PBRT).

The major push for particles beyond protons comes from the unique biology associated with these heavier particles. In addition to the dose distribution advantages associated with PBRT the adoption of higher linear energy transfer (HiLET), particles such as Carbon yield an increased level of effectiveness against hypoxic (poorly oxygenated) tumor cells. These represent the most radiation and chemotherapy resistant aggressive tumor cells—are killed more efficiently with HiLET ion beams than with photons. In adults, tumors of lung, the head and neck, brain, base of skull, soft-tissues and eye, may especially benefit from the advantages of HiLET particle beam therapy.

More Effective & Cost Effective?

Studies performed to date suggest that the use of HiLET particle beams for cancer treatment may be more effective and more cost effective than PBRT [16, 19, 20]. However, to justify the development of such a facility extensive R&D and a formal cost-effectiveness assessment are needed in order to maximize the benefits to the US health care system from these therapies. Studies comparing the effectiveness of proton, photon and carbon ion therapy in a number of situations where hadron therapy is expected to have a clear advantage have yet to be conducted. More basic biological studies are needed to characterize such situations—for example, in hypoxic tumors. Clinical physics research is needed to not only streamline treatment and develop improved techniques for beam delivery but to assess the environmental impact. Such a study will need to address issues such as energy consumption needs and potential radioactive waste disposal. To optimize the opportunities for success in this endeavor extensive R&D resulting in improvements in basic accelerator research technology will reduce the equipment's complexity and cost. The clinical and technical R&D will need to be conducted both collaboratively with industry and independently so as not to hamper innovation. This means that vendors will be involved in producing various components but to new specifications reflecting fundamental breakthroughs will more likely come from an integrated blend of the talents of accelerator experts and medical professionals.

Requirements for the San Francisco Particle Research Center (SPARC)

In addition to the socioeconomic and clinical research related goals alluded to above, the following are additional practical requirements:

1. The PRC must be situated at a convenient location for all the partners.
2. The PRC must be capable, from its inception, of producing protons and carbon ions.
3. By virtue of its design and its business model, the PRC must support treatment for tumors at a wide variety of sites within the body, and offer comprehensive treatment for pediatric patients.
4. The PRC must be designed from the outset to allow for an extensive program of both clinical and accelerator R&D.
5. The partner institutions must control the scheduling and utilization of the facility. Thus, we are strongly against a funding plan that cedes operational control of the PRC to a third-party equity partner.
6. SPARC stands strongly recommended against a facility limited to protons and acknowledges there may be a need to first establish routine treatment with protons before starting carbon therapy, but the R&D program will benefit from having access to carbon beams from the start.
7. For financial and other considerations, it is tempting to consider a plan that starts with a facility that has proton capability only and then "upgrades" to carbon. However, any changeover would be radical, very expensive and potentially disruptive to the proton therapy program so this approach is not favored.

What R&D Program and What Layout?

After extensive discussion and research the SPARC members favored the follow characteristics of the R&D work:

1. We unanimously agreed that we should use a synchrotron-based system because it provides variable energy, which in turn facilitates active scanning and obviates the need for energy degraders.
2. We also favored the development of a high-gradient microwave-driven proton linac and/or the development of a plasma deflagration gun (in the future).
3. The final layout of the three-story building was done by a professional institutional planner, who was able to bring substantial critical appraisal to the design. Its configuration is compact, yet incorporates four treatment rooms sized for both carbon and proton treatment, a large research space.
4. The layout includes an R&D experimental vault that can accommodate multiple beam-lines, and a generous allotment of space for activities that support treatment, facility operation, and R&D.

Progress

On September 1, 2010, a meeting was held to discuss establishment of SPARC and included representatives from all of the key Bay Area stake-holders. The meeting was hosted by Phil Pizzo, Dean of the Stanford School of Medicine, and co-Chaired by Sam Hawgood, Dean of the UCSF School of Medicine. Participants included physicians and physicists from UCSF (Peter Carroll, MD, Mack Roach, MD) and Stanford (Sarah Donaldson MD, Amato Giaccia MD, Richard Hoppe MD, Quynh Le MD, Michael Link MD, and Lei Xing PhD), representing the Departments of Radiation Oncology and the Cancer Centers, Senior Scientists from LBNL (Dave Robin PhD, Joe Gray PhD, and Steve Gourlay PhD), and from SLAC Eric Colby PhD, Persis Drell PhD and Jonathan Dorfan and hospital representatives from Packard Children's Hospital (Chris Dawes and Jim McCaughey), SHC (Sri Seshadri and Mike Peterson), and UCSF (Jay Harris).

There was general agreement that 1) hadron therapy had an important clinical role for the management of children with cancer; 2) hadron therapy had a potential important role in the management of many adults with cancer; 3) important clinical research (clinical trials) was essential to defining the ultimate utility of hadron therapy; 4) the potential for Carbon ion therapy remains largely unexplored; 5) there are key concepts of hadron beam generation that would benefit from basic research to make this therapy more widely available; 6) the success of such a venture would be most likely if a partnership as described above could be developed. There was also agreement that the combined talent present in Bay Area institutions made Northern California an ideal location to develop hadron therapy and that Carbon therapy was an essential component of that plan. Indeed there is no other part of the USA or indeed the world that has such a unique regional collection of basic, applied and clinical talent.

The primary challenge to realizing SPARC relates to financing. The immediate action item was to investigate funding sources and evaluate support for such a plan from important constituencies at the Federal level. With that in mind, the government affairs groups at each of the four institutions will initiate discussions and craft a plan for moving forward. This will require assessing the landscape of state and federal public sources and develop a plan for educating and alerting federal agencies and Congress.

SPARC: the Business Plan and Next Steps

By far the biggest challenge to realizing a Particle Radiation Center is the initial capital cost. At this juncture we are evaluating a preliminary goal of acquiring approximately $80 to 100 million of public sector funding with the understanding that approximately $80 to 120 million will come from the four institutions. The Task Force estimated that a facility with the requirements discussed in the section above required a capital outlay of approximately $200M (FY 2009 accounting). This effort includes the development of strategies to ensure that the treatment function is financially sustainable. To assess this issue, a business sub-group was commissioned by the Advisory Board Company to provide "guidance in developing a viable and sustainable business plan around opportunities for investing in a particle therapy center." The Advisory Board produced a comprehensive, well-researched and well-documented set of reports that provide financial and market analyses covering a wide range of assumptions regarding the corporate structure and cost sharing.

A viable capital-funding plan will have to be built from multiple sources, including existing funds, debt, third-party financing, Federal funds or State funds, and philanthropy. An equal-share partnership among the institutions would significantly ease the burden of raising the initial capital. Stanford, UCSF, SLAC, and LBL are moving forward with SPARC, by attempting to raise funds in excess of $200M. The major sources are expected to come in order of preference from (1) several Federal sources; (2) State and Local Governmental Agencies; (3) Private Foundations; (4) through Philanthropic endeavors; (5) through contributions from both Hospitals and Medical institutions and; (6) with Private Investors filling in the remaining need. The Task Force identified two primary objectives to be coordinated: a) the development of a credible funding plan and the identification of the funding sources, and b) the formation of a team of clinicians, physicists and engineers to generate, and document, a mature design for the PRC. The TF recommended that a SPARC Proposal Office (SPARCPO) be formed to coordinate these processes.

Timeline

Our next conference call is scheduled for December 9th at which time we are hopeful that details of our timeline will be solidified and tasks delegated. The timeline to realize SPARC is estimated to be approximately five years. The first one-and-a-half years is foreseen to include: a) develop research collaboration teams; b) complete a design in collaboration with a vendor and c) to raise the capital investment. The construction/commissioning phase will be three-and-a-half years.

Conclusions

There exists a body of evidence that heavy charged particles have the potential to be more effective and more cost effective than other forms of external beam radiation, including Proton based therapy. A joint venture is underway between Stanford and UCSF in conjunction with two large physics research institutions, SLAC and LBNL to build an advanced particle therapy center in the San Francisco bay area.

Table 1. Collaborative Working Partners: SPARC

Sub-Group	Potential Investigators	Purpose
Governance	Pizzo, Hawgood, Dawes	Coordinate Governance development
Finance	Pizzo, Hawgood, Harris, Seshadri, Laret, Rubin …	Coordinate SOM budgetary issues Coordinate hospital budgetary issues
Cost-effectiveness research	Brindis, Owens and others?	Help lead cost effectiveness research component
Clinical Trials	Roach, Hoppe, Le …	Define appropriate trials to test value of Particle therapy
Accelerator Design	Gourlay, Colby, Robin …	Lead novel accelerator design
Radiobiology	Blakley, Giaccia, Munane …	Biologic modeling and animal studies

SPARC=San Francisco Bay Area Particle Accelerator Center; SOM=School of Medicine; SUMC= Stanford University Medical Center; UCSF=University of California San Francisco; SLAC=Stanford Linear Accelerator Center; TBD=to be determined.

Table 2. Summary of Major Funding Sources for SPARC*

Source	Amount / Goal	Purpose/Goal/ Status
SUMC/SLAC	$500,000 / same	Detailed feasibility study. Completed
Depart of Radiation Oncology UCSF	$165,000 / same	Long term follow-up on patients treated by UCSF faculty at LBNL. Ongoing
NCI	80 – 100M	Request pending
Philanthropy	40 to 100M	Efforts pending
Stanford University Medical Center	25M / same	Efforts pending
UCSF Medical Center	25M / same	Efforts pending
DOE	50M / same	
AHRQ	5M / same	Efforts pending
Vendor Support	20M / same	Efforts pending
Private investors	40M / TBD	Efforts pending
Other	20M / TBD	
Total	**$665.000 / ~200M**	Total amount required to develop research infra-structure and design and build SPARC according to specification

SPARC=San Francisco Bay Area Particle Accelerator Center; SUMC= Stanford University Medical Center; UCSF=University of California San Francisco; SLAC=Stanford Linear Accelerator Center; TBD=to be determined.

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DAY 2: Thursday, 13 January

Skull Base and Head-and-Neck Tumors

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Summary

Carbon ion radiotherapy, with its powerful biological effects, provides excellent therapeutic efficacy for patients with radioresistant tumors. By focusing the irradiation beam on the target lesion, this approach guarantees a low probability of damage to critical organs (e.g., brain, spinal cord, eyes, optic nerves) in the immediate vicinity of the target tumor. Regarding tumors in the head and neck region, carbon ion radiotherapy is indicated for the treatment of chordomas of the skull base and the first and second cervical vertebrae, as well as adenoid cystic carcinomas, adenocarcinomas, and malignant mucosal melanomas in the maxillofacial district. The safety and efficacy of this therapy have been established. There are certain groups of radioresistant tumors that are not indicated for surgical resection because of possible surgery-induced injury to critical organs, and these tumors raise a significant clinical concern because of the paucity of effective treatment options. We expect that carbon ion radiotherapy will represent a definitive treatment for these malignancies.

Introduction

It is often difficult to completely eradicate malignant tumors of the skull base or the head-and-neck region by surgery alone, owing to their location or progression. Radiotherapy is the first-line treatment of choice for most of these tumors. However, in the head and neck region, various types of non-squamous cell tumors develop that are not sensitive to photon radiotherapy (x- and γ-rays). Dose restrictions for the critical organs located in the proximity of the target lesion (e.g., brain, brain stem, spinal cord, eyeballs, optic nerves) prevent the administration of sufficient therapeutic radiation doses. For these reasons, a considerable proportion of cases of non-squamous cell neoplasms of the head-and-neck region are diagnosed as intractable, yielding poor local control rates.[1-13)]

In June 1994, the National Institute of Radiological Sciences initiated a clinical trial of heavy charged particle therapy for malignant head and neck tumors. For these tumors, the radiation oncologist has clear access to the reactions of the adjacent skin and mucous membrane that serve as dose-limiting factors. The carbon ions have the excellent dose localization due to the physical characteristic commonly known as the Bragg peak. The carbon ions also have been demonstrated to have beneficial biologic effects against tumors. [14)] Because of these

features, carbon ion radiotherapy has been expected to provide an effective tool for the treatment of radioresistant tumors, and its safety and effectiveness have been established for tumors in various sites.[15-17] We herein review the results of studies of carbon ion therapy for intractable head-and-neck tumors.

1. Skull Base and Paracervical Tumors

Patients and Methods

A phase I/II dose-escalation study was carried out from April 1997 to February 2004. Chordoma, meningioma, chondrosaracoma and other tumors originating from the skull base or paracervical spine located superior to the C2 vertebra were targeted in this study. The treatment regimen consisted of 16 fractionations over four weeks, with a total dose of 48 GyE, which was increased by 10% four times in a step-wise manner. Based on the results of this study, a new clinical study was initiated in April 2004 under the government-initiated Highly Advanced Medical Technology program, with an irradiation schedule delivering a total dose of 60.8 GyE in 16 fractionations over four weeks. Between April 1997 and February 2010, a total of 67 patients were treated: 39 with chordomas, 12 with chondrosarcomas, eight with olfactory neuroblastomas, seven with meningiomas, and one with a giant cell tumor. Acute toxicity was assessed based on the Radiation Therapy Oncology Group (RTOG) score, and late toxicity was determined based on the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) score. Local control and overall survival rates were calculated according to the Kaplan-Meier method.

Results

Acute skin and mucosal reactions were of a minor nature, as one patient in the 48 GyE group showed a grade 3 skin reaction with confluent moist desquamation, one patient in the 57.6 GyE and 2 patients of the 60.8 GyE groups showed a grade 3 mucosal reaction with a confluent pseudo-membrane that necessitated opioid-mediated pain control. However, all of these cases evolved later to grade 0 or grade 1 reactions including mild atrophy, pigmentation, and mucosal dryness. The observed late reactions involved no grade 3 or higher atrophy, telangiectasia, or other serious adverse reactions. No acute reactions developed in the brain or spinal cord. With regard to late reactions, three of 64 eligible patients (5%) developed grade 2 encephalitis, which required temporary administration of steroids; however, no other adverse reactions were reported for the brain or spinal cord. The 5-year local control and overall survival rates were both 86% for all histological types, whereas the rates were 82% and 89%, respectively, for the largest subcohort of 39 patients with chordomas.

Further, the 5-year local control and overall survival rates were 95% and 90%, respectively, for the group of 29 chordoma patients irradiated with 60.8 GyE. Two of these 29 patients died within five years after treatment; their causes of death were peripheral recurrence for one and hepatic failure (unrelated to the tumor of concern) for the other.

2. Head-and-Neck Malignant Tumors

Patients and Methods

Two phase I/II clinical trials of different fractionations were performed from June 1994 to February 1997 for malignant head-and-neck tumors. Based on the outcome of these two studies, a subsequent phase II clinical trial was started in April 1997. The treatment dose was 64.0 GyE in 16 fractions over 4 weeks (or 57.6 GyE when a wide area of skin and/or mucosa was included in the target volume). Between April 1997 and February 2010, a total of 378 patients were treated, consisting of 129 patients dosed with 64.0 GyE and 249 patients dosed with 57.6 GyE. Histologically, the tumors were classified as follows: 134 with adenoid cystic carcinoma, 102 with malignant melanoma, 46 with adenocarcinoma, 22 with squamous cell carcinoma, 14 with mucoepidermoid carcinoma, 14 with osteosaromas and other types of bone and soft-tissue sarcomas, 13 with papillary adenocarcinoma, 7 with undifferentiated carcinoma, 6 with osteosarcoma, and 6 with acinic cell carcinoma. There were five cases of T1, 31 of T2, 58 of T3, 161 of T4 stage, and 123 with a recurrent tumor after surgery and/or chemotherapy.

Results

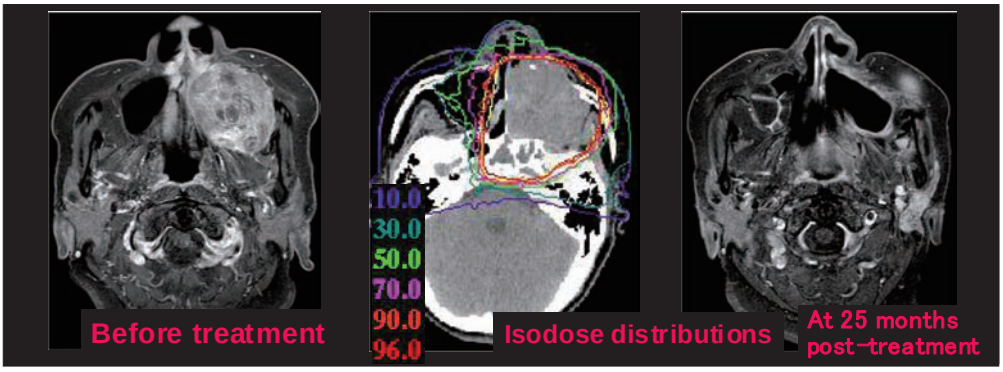
Acute reactions were of a minor nature, as 15 patients (4%) showed a grade 3 skin reaction, and 59 patients (16%) showed a grade 3 mucosal reaction. The late toxic reactions were comprised of a grade 2 skin reaction in 8 patients (2%) and mucosal reactions in 12 patients (3%), with no evidence of radiation-induced toxicities worse than these. This therapy can therefore be described as presenting no clinically-significant problems. The recorded tumor-related events included optic neuritis, encephalitis, sinusitis, otitis media, and maxillary bone necrosis that needed surgical treatment. These events were documented in patients who had been informed before the start of therapy about the possibility of adverse events due to tumor infiltration. Other patients reported no unexpected serious adverse reactions.

The 5-year local control rates according to major histological types were as follows: 79% for adenocarcinomas; 81% for adenoid cystic carcinomas (see Figure 1 for a typical case representation); 78% for malignant mucosal melanomas (see Figure 2 for a typical case representation); and 73% for squamous cell carcinomas. However, 14 patients with bone and soft-tissue sarcomas in the head-and-neck region (mostly osteosarcomas) had a poor 5-year local control rate of 24%, although the majority of the patients received 64 GyE. Consequently, a new treatment protocol was started in April 2001 to apply a total irradiation dose of 70.4 GyE in 16 fractionations over four weeks for these patients, a schedule similar to that for the treatment of bone and soft-tissue sarcomas of the trunk. By the end of February 2010, 35 patients had been treated; none of them demonstrated any unexpected adverse reactions, and the 5-year local control rate was 83%, showing an excellent therapeutic effect.

Additionally, the 5-year overall survival rates from the initial two trials were 66% for adenocarcinomas, 72% for adenoid cystic carcinomas, and 36% for malignant mucosal melanomas. Although the local control of carbon ion radiotherapy was promising for malignant mucosal melanoma. The survival rate was not commensurate with the favorable local control rate because of subsequent regional lymph node or distant metastases. Based on the results of the preliminary analysis of this study, a new protocol was started in April 2001 for the purpose of prophylactic therapy against distant metastasis, the major cause of death in malignant melanoma of the head-and-neck region. This new protocol is intended to prevent metastases, and it has also led to an improvement in the 5-year overall survival rate to 64%.

Isodose curves: red = 96%; pink = 60%; green = 50%; blue = 30%; purple = 10%; yellow = clinical target volume

Figure 1. Adenoid cystic carcinoma of the paranasal sinus (target volume: 262 mL)
A 34-year-old male, treated with carbon ion radiotherapy at a total dose of 57.6 GyE in 16 fractionations over four weeks. Pre-treatment Gd-DTPA-enhanced T1-weighted images depicted a tumor filling the nasal cavity, ethmoid sinus, and sphenoid sinus, and extending into the anterior cranial fossa. No tumor was visible at 27 months after treatment. Although the irradiated tumor was located in close proximity to the optic chiasm, the patient retained bilateral visual acuity.



Isodose curves: red = 96%; pink = 70%; green = 50%; blue = 30%; purple = 10%; yellow = clinical target volume

Figure 2. Malignant melanoma of the paranasal sinus (target volume: 275 mL)
A 63-year-old female, treated with carbon ion radiotherapy at a total dose of 64 GyE in 16 fractionations over four weeks and concurrent chemotherapy with dacarbazine, nimustine hydrochloride, and vincristine. Pre-treatment MRI images revealed a tumor in the left maxillary sinus and the orbital floor and invading the palatal bone. The patient developed well-defined bone necrosis. Since the tumor was locally controlled and the necrotic bone was locally limited, surgical resection of necrotic bone was performed for pain control. A denture and palatal prosthesis were successfully applied.

Discussion

As the efficacy of carbon ion radiotherapy for chordoma and other types of skull base tumors can only be judged on the results of long-term prognosis, it will take more time to determine the definitive conclusions.

If our current results should continue for 10 or more years, they would indicate that this regiment represents an optimal management strategy for adverse reactions and a better local control than the photon- and proton-based radiotherapies.[1-6] Non-squamous cell locally advanced tumors are generally considered to be poor candidates for photon radiotherapy and/or chemotherapy, however, carbon ion radiotherapy showed excellent therapeutic effectiveness in these preliminary results.[7-13] The carbon ion radiotherapy will likely prove to be beneficial as a first-line local treatment for advanced tumors that are not indicated for surgery and are likely to be refractory to conventional radiation treatment.

High linear energy transfer (LET) charged particles, such as carbon ions, have excellent dose localizing properties, and this potentiality can cause severe damage to the tumor while lessening the effects on normal tissue. When the tumor was located close to critical organs in the present studies, delineation of the clinical target volume was done with efforts to spare these organs. In particular, when the eyeball and/or optic nerve were involved in the high-dose area, treatment planning was performed to spare the contralateral optic nerve and chiasm, according to our previous dose criteria. [19,20] Efforts are being made to decrease adverse reactions by clinically applying the results of these studies.

Conclusion

The safety and efficacy of carbon ion radiotherapy have been established for malignant head-and-neck tumors. Further improvements in the local control and survival rates are an important challenge for the scientists engaged in studying carbon ion radiotherapy.

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Carbon Ion Radiotherapy for the Treatment of Hepatocellular Carcinoma

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Summary

The treatment of hepatocellular carcinoma (HCC) associated with underlying chronic liver diseases should include every possible effort to maintain optimal liver function. Charged particle therapy using proton and carbon ion beams provides a sharper and more focused irradiation to the target region of the liver than conventional X-ray radiotherapy. It therefore reduces the risk of treatment-related liver damage. A series of four clinical studies of carbon ion radiotherapy for the treatment of HCC were conducted at the National Institute of Radiological Sciences form June 1995 to Augst 2005. These studies determined the optimal doses for radiotherapy for HCC. We also contributed to reducing the number of irradiation sessions, and achieved a shorter treatment period. The treatment schedule was simplified from 15 fractions over five weeks to two fractions for two days. The local control rates for the carbon ion radiotherapy were around 90% across various tumor sizes, tumor locations, and fractionations schedule. In most of the patients, the liver function showed no or a minor deterioration. Heavy charged particle therapy, which provides a safe and powerful therapeutic modality for tumors of all sizes, is an excellent choice for the treatment of HCC. It can be used effectively in conjunction with other approaches available in multidisciplinary disease management.

Introduction

Hepatocellular carcinoma (HCC) is most likely to accompany chronic liver diseases resulting from persistent infection with hepatitis B or C viruses, and notably, liver cirrhosis. Patients presenting with HCC, therefore, often have compromised liver function. Liver cirrhosis is frequently associated with synchronous or metachronous multiple primary tumors, which thus require immediate intervention. Under these conditions, it is important to sustain the remaining liver function to the greatest extent possible while treating the HCC.

The major approaches for the treatment of HCC include surgical resection, percutaneous local therapy, and transcatheter arterial chemoembolization (1). Although surgical resection offers a high curative probability, it places a significant burden on the patient. It is generally recommended for patients with localized tumors and relatively intact liver function. In addition, a considerable proportion of patients are often ineligible for this type of intervention.

Percutaneous local therapies, including radio-frequency ablation and ethanol injection, achieve excellent results for small tumors, but the efficacy of these therapies diminishes with increasing tumor size. These therapies are limited not only in the size and number of target tumors (2, 3), but also in technical applicability.

Transcatheter arterial chemoembolization can be used for the treatment of relatively large tumors and multiple lesions (4). However, this approach has a poor prognosis for tumors involving extracapsular infiltration and portal vein thrombosis (5). Patients will often have to undergo repeated courses of this therapy, due to its insufficient anti-tumor effect.

An early report of serious hepatic injury by whole liver irradiation (6) led to the irradiation dose being decreased to a level below the dose sufficient for exerting anti-tumor effect. Consequently, radiotherapy was not commonly used for the treatment of HCC until recently. However, recent advances in irradiation technology have opened the door for selective irradiation centered on a specific and narrow region of the liver. Clinical studies have reported diminished tumor size and prolonged survival in HCC patients treated with high-energy x-ray radiotherapy (7-9). Studies have also demonstrated excellent local tumor effects and long-term outcomes in patients treated with charged particle therapy using proton and carbon ion beams, which provide sharper and more focused irradiation than both conventional high-energy x-ray radiotherapy (10-17).

In addition to the excellent dose localization profile, heavy charged particle beams such as carbon ion beams are known to have exert stronger biological effects than proton and x-ray beams (18-20). Heavy charged particle therapy is thus expected to provide a definitive and minimally invasive technique for the treatment of HCC. The following sections describe the details and results of the clinical studies of carbon ion radiotherapy for HCC carried out at our institution.

Outline of the Clinical Studies

A successive series of clinical studies of carbon ion radiotherapy for HCC were started in June 1995 (11). The first phase I/II study was carried out to determine the optimal dose for the schedule of 15 fractions given in five weeks, based on a dose-escalation protocol. The irradiation doses were increased by 10% several times after confirming the safety and efficacy of the therapy. The subsequent phase I/II study was conducted not only to determine the optimal dose, but also to explore the possibility of reducing the number of fractions and hence the duration of the treatment period. This study showed that the duration of therapy could be reduced to three weeks of 12 fractions and then to one week of four fractions. Following the outcomes of this study, a phase II study was launched, which administered a fixed total dose of 52.8 GyE divided into four fractions of 13.2 GyE. The results of this study confirmed the safety and efficacy of this regimen (12). All of these studies enrolled a large majority of patients with HCC that had relapsed after, or was refractory to, other therapies, and those judged as non-responsive to conventional therapies. In addition, a separate phase I/II study was conducted, which adopted a short-term regimen of two fractionations in two days (13). At present, our hospital is providing short-term irradiation therapy under the government-sponsored Highly Advanced Medical Technology program.

Results of the Clinical Studies

The following paragraphs present the results obtained by the end of the phase II study that applied the 4-fraction regimen; the results included patients that were followed up for 5 or more years.

1. Anti-tumor Effect

In the majority of patients administered the heavy charted particle therapy, shrinkage of tumor size will start within several months after the therapy, and terminate in approximately one year. Only a minor proportion of patients will achieve complete tumor response, and a larger portion of patients will experience a lesser anti-tumor response. For this reason, it is more appropriate to evaluate the anti-tumor effect of the heavy charged particle therapy for HCC in terms of local control, rather than tumor response. Table 1 depicts the local control rates by study protocol and number of fractions. The 1-, 3-, and 5-year local control rates were in the range of 89%–98%, 81%–95%, and 81%–95%, respectively. The results showed no significant difference in outcome between the numbers of fractions. However, irradiation of shorter duration tended to yield a higher local

control rate, thus suggesting that the treatment period could be shortened without compromising the therapeutic effect. No significant difference was noted in the local control rate by tumor size or location (Figure 1) (17).

Table 1. The Results of Clinical Studies of Heavy Charged Particle Therapy for the Treatment of Hepatocellular Carcinoma

Study phase	I/II		I/II		II
Study period	1995.4-1997.2		1997.4-2001.2		2001.4-2003.2
Fractions/treatment period in weeks	15/5	12/3	8/2	4/1	4/1
Total dose (GyE)	49.5-79.5	54.0-69.6	48.0-58.0	48.0-52.8	52.8
No. of tumors	24	34	24	28	47
(Post-treatment recurrences)	□ (18)	□ (18)	□ (16)	□ (18)	□ (20)
Tumor diameter (cm)	2.1-8.5	1.5-7.2	1.2-12.0	2.2-12.0	1.2-7.5
Median tumor diameter (cm)	(5.0)	(3.7)	(3.1)	□ (4.6)	□ (3.7)
1-Year local control rate (%)	92	97	91	89	98
3-Year local control rate (%)	81	86	86	89	95
5-Year local control rate (%)	81	86	86	89	95

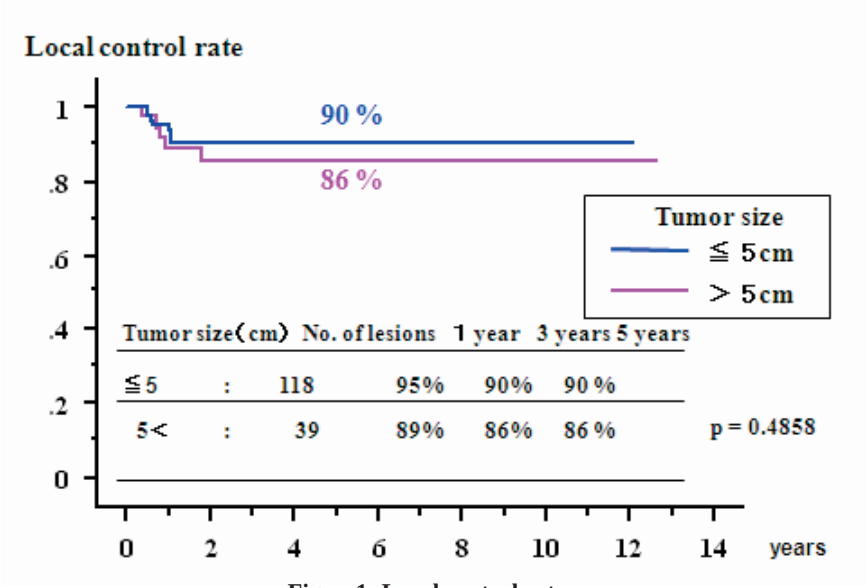


Figure1: Local control rate

2. Adverse Events

These studies reported no cases of treatment-related deaths or liver failure directly caused by the therapy. In order to evaluate the effect of carbon ion radiotherapy on liver function, changes in the Child-Pugh score from

baseline were assessed and compared. The Child-Pugh score, a clinical measure for determining the degree of liver injury, evaluates hepatic damage on a 5- to 15-point scale. The results indicated that while an increase in the score suggested a general trend toward hepatic failure, the majority of patients had a score change of one point or fewer, with respect to both acute (within three months after therapy) and late (later than three months following therapy) reactions (Figure 2). These findings revealed that the hepatic damage was mild for most patients. The proportions of patients whose score increased from baseline by two or more points due to late reactions (which have a high clinical relevance) tended to be smaller with a smaller number of fractions. These results showed that shortening the treatment period enhanced the treatment safety in terms of the incidence of adverse events. No serious adverse events were reported in the skin, gastrointestinal tract, or other perihepatic tissues and organs.

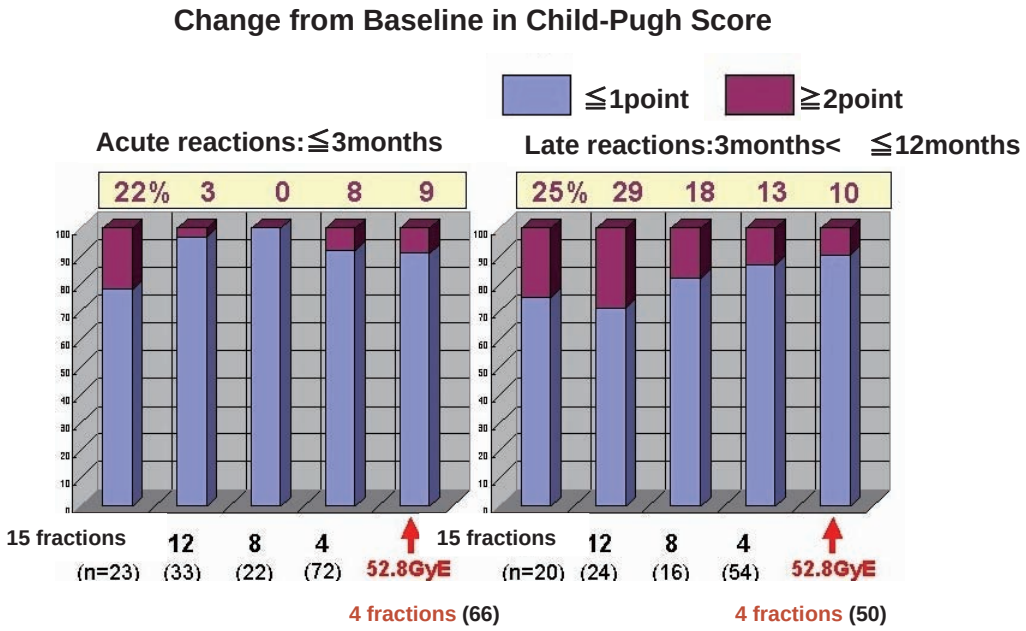


Figure 2: Changes in Child-Pugh score

3. Survival Rates

Among the treatment regimens used in the clinical studies, the 4-fraction irradiation of 52.8 GyE was administered to the largest number of patients. For the patients that underwent this regimen and had no lesions outside the radiation field, the 1-, 3-, and 5-year cumulative survival rates were 94%, 64%, and 37%, respectively. When the analysis was limited to the patients that developed a solitary tumor with a maximum diameter in the range of 3 to 5 cm, and had a well-compensated liver function (Child-Pugh grade A), the 1-, 3-, and 5-year cumulative survival rates were 88%, 75%, and 63%, respectively. These results were comparable to the outcomes of hepatectomy (Figure 3) (1). For all study patients with tumors of 7 cm or larger in diameter and well-compensated liver function, the 1-, 3-, and 5-year cumulative survival rates were 95%, 64%, and 27%, respectively. These results were also comparable to the outcomes of hepatectomy (1).

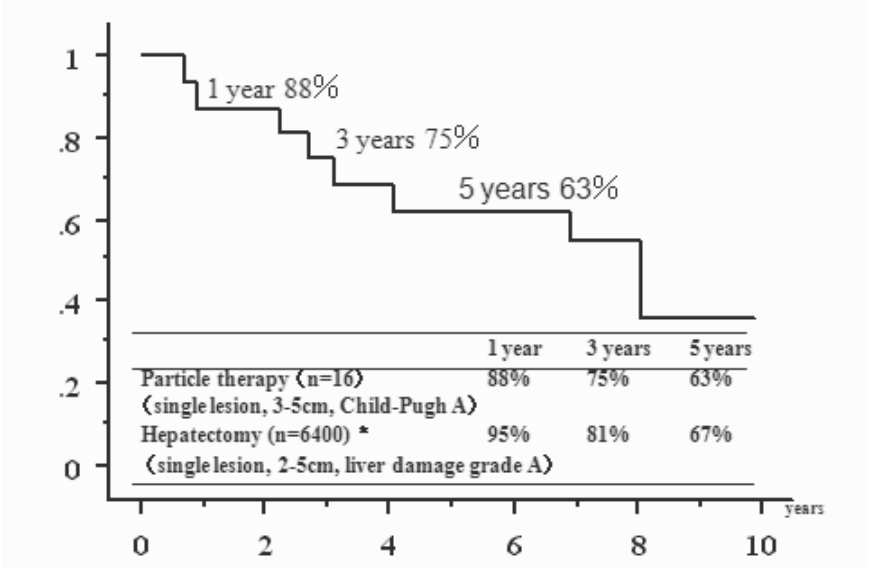
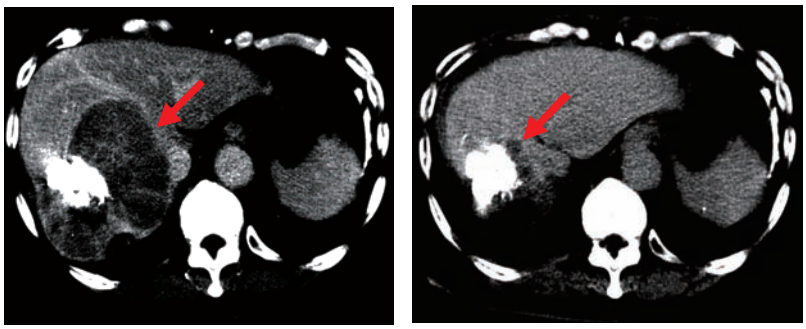


Figure 3: Overall survival rate in patients with 3-5 cm solitaly tumor and Chid-Pugh grade A liver functioni

Patients Recommended for Heavy Charged Particle Therapy

It is difficult to completely eradicate a tumor by heavy charged particle therapy alone in patients with too extensive tumor infiltration or with multiple tumors. The heavy charged particle therapy is most suitable for patients with localized lesions and moderate or higher liver function (Child-Pugh grade A or B)High local control rates can be attained for tumors measuring 3 cm or smaller in diameter when treated with surgery or percutaneous local therapy. Therefore, patients with a tumor of this size range that cannot be treated using these modalities for some reason are recommended for heavy charged particle therapy. It is quite difficult to control large tumors exceeding 3 cm in diameter by percutaneous local therapy alone. These tumors are thus considered to be indicated for either surgery or heavy charged particle therapy. However, heavy charged particle therapy is contraindicated for patients whose tumor is located in close proximity to the gastrointestinal tract, from the viewpoint of protection against irradiation damage. In addition, patients with uncontrollable ascites are not suitable for this therapy, because of the difficulty in ensuring precise irradiation.



A B

Figure 4: CT scan of a 71-year-old man with huge HCC before(A) and 1 year after(B) the treatment

Conclusion

Heavy charged particle therapy, which provides a safe and powerful therapeutic modality for tumors of

various sizes, is an excellent choice for the treatment of HCC. It can be used effectively in conjunction with other approaches in multidisciplinary disease management.

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Carbon Ion Radiotherapy for Locally Advanced Cervical Cancer

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1. Introduction

The definitive treatment for cervical cancer includes surgery and radiotherapy, which are often combined with chemotherapy. Appropriate therapy will be chosen, based on overall evaluation of the clinical stage and the histology of the tumor, as well as the patient's age and the presence or absence of concomitant disease. Stage I or II disease with small cervical tumor is commonly indicated for surgery or conventional radiotherapy, and these procedures have yielded excellent treatment results. However, stage II disease with large tumor and stage III or IVA disease are generally unresectable, and the standard treatment for these tumors is the combination of radiotherapy and chemotherapy (i.e., chemoradiotherapy).

Conventional radiotherapy for cervical cancer combines external high-energy x-ray irradiation to the pelvis and intracavitary brachytherapy by placement of small-sized radioactive sources into the uterus and vagina. External irradiation covers the primary tumor as well as the parametrium and pelvic lymph nodes, which may possibly involve tumor infiltration or metastasis. Intracavitary brachytherapy delivers a very high dose to the cervical tumor with minimizing the dose to the surrounding normal tissues.

However, conventional radiotherapy is frequently insufficient for the treatment of extensive and large tumors; such tumors will often recur locally, despite treatment with chemoradiotherapy. Therefore, the treatment of huge tumors (with diameter exceeding 5 or 6 cm) should include new therapeutic approaches. Tumor histology is an important prognostic factor. Advanced adenocarcinomas have poorer outcomes compared with squamous cell carcinomas. It is partly accounted for by the fact that adenocarcinomas are more radioresistant than squamous cell carcinomas, being less prone to adequate local control. These observations underscore the need for establishing new therapeutic strategies for advanced cervical adenocarcinoma.

In order to improve outcomes for the treatment of advanced cervical cancer that cannot be adequately controlled by conventional radiotherapy, the National Institute of Radiological Sciences (NIRS) started the clinical studies using carbon ion radiotherapy in 1995.

2. Carbon Ion Radiotherapy for Advanced Cervical Cancer

Carbon ion radiotherapy was indicated for cervical cancers meeting the following inclusion criteria: (1) locally advanced stage IIb to IVa disease, (2) medically inoperable, (3) tumor diameter of 4 cm or

greater, (4) negative abdominal para-aortic lymph node metastasis assessed by CT, (5) absence of rectal tumor infiltration, (6) patient age: 20 to 80 years, (7) absence of serious concomitant disease, and (8) no previous history of surgery, radiotherapy, or chemotherapy.

The treatment consisted of whole pelvic irradiation and local boost, with the target volume being shrunk in three steps so that the highly concentrated dose could be delivered to the tumor without increasing the dose to normal structures. The clinical target volume (CTV) for whole pelvic irradiation included all areas of gross and potentially microscopic disease, consisting of the primary tumor, uterus, parametrium, at least the upper half of the vagina, and pelvic lymph nodes. After completing whole pelvic irradiation, local boost irradiation was performed. First, CTV included the gross tumor volume and surrounding tissues, such as the parametrium, uterine body, upper vagina, and adjacent lymph nodes (extended-local irradiation). Next, CTV was further shrunk to GTV only (local irradiation), and the intestines and bladder were completely excluded from the target volume. Carbon ion radiotherapy was given once daily, 4 days per week, for a fixed 20 fractions in 5 weeks, consisting of three weeks of whole pelvic irradiation and one week each of extended-local and local irradiation. Because most cervical tumors diminished in size during treatment, the CTVs of both extended-local and local irradiation were defined based on the findings of pelvic exams and sequencial CT and MRI.

3. Results of Carbon Ion Radiotherapy for Advanced Cervical Cancer

The NIRS has conducted four dose-escalation clinical studies to investigate the safety and efficacy of carbon ion radiotherapy for locally advanced cervical cancer. Consequently, the following conclusions were drawn on safety: (1) whole pelvic radiotherapy delivering 36–39 GyE in 12–13 fractions could be performed safely without severe acute toxicity, and (2) the total dose of the intestinal tract should be kept below 60 GyE, as indicated by the analysis of the serious late toxicities of the intestinal tract observed in the first two clinical studies. As a result of improvement made in the irradiation techniques according to these conclusions, there has been no serious late intestinal toxicity for recent seven years.

Regarding effectiveness, the following clinical observations were made: (1) whole pelvic irradiation of 36–39 GyE in 12–13 fractions adequately suppressed lymph node recurrence in patients presenting no apparent lymph node enlargement by diagnostic imaging, suggesting that such dose level is sufficient for controlling microscopic lymph node metastasis, and (2) the local control rate increased with the total dose, and doses of around 72 and 68–74.4 GyE were necessary for the local control of squamous cell carcinoma and adenocarcinoma, respectively.

Figure 1 illustrates the results of carbon ion radiotherapy for stage IIIb to IVa cervical squamous cell carcinomas. All patients received a high-dose irradiation of 72–72.8 GyE to the cervical lesion. Although the patients had a mean tumor diameter of 6.7 cm, the 5-year local control rate was as high as 83%. The 5-year overall survival rate was 52%, and distant metastasis was the leading cause of death. Studies on chemoradiotherapy for stage III or IVa cervical cancers reported 5-year local control rate at around 70% and 5-year overall survival rate at 56%–59%. In light of the fact that a significant

proportion of patients administered carbon ion radiotherapy had very huge tumors, and were not indicated for chemotherapy due to high age or concomitant diseases, the outcomes of this therapy seemed comparable to those of chemoradiotherapy. Because many treated patients developed abdominal para-aortic lymph node metastasis, we are currently performing a clinical trial of prophylactic para-aortic irradiation using carbon ion radiotherapy.

Figure 2 represents the results of carbon ion radiotherapy for stage IIIb to IVa cervical adenocarcinomas. All patients received a high-dose irradiation of 68-74.4 GyE on the cervical lesion. Despite the inclusion of several cases with a short follow-up period, the 2- and 5-year local control rates were 88% and 68%, and the 2- and 5-year overall survival rates were 61% and 55%, respectively. Although the number of studies reporting the outcomes was limited, the incidences of local recurrence and distant metastasis were both high for patients with advanced cervical adenocarcinoma, and the 5-year local control and overall survival rates for stage III patients were reported to be as low as 46% to 58% and 0% to 29%, respectively. When compared with these results, carbon ion radiotherapy seemed to yield excellent outcomes at present. However, our results showed that the local control rate for cervical adenocarcinoma was poorer than that for squamous cell carcinoma, and the incidence of distant metastasis was higher in patients with cervical adenocarcinoma than those with squamous cell carcinoma. We have therefore initiated a clinical study on the combination of carbon ion radiotherapy and concurrent chemotherapy in patients with advanced cervical adenocarcinoma.

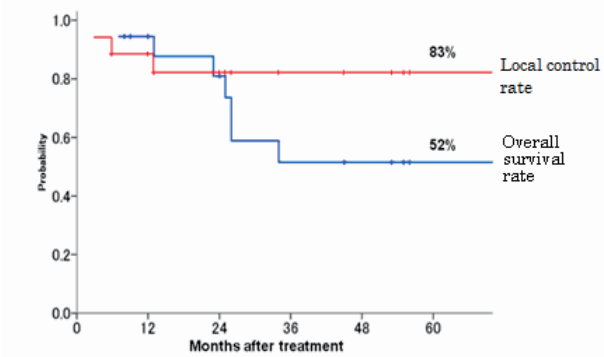

Figure 1. Results of heavy charged particle therapy in patients with cervical squamous cell carcinoma (n = 18; stage: IIIb to IVa; dose: 72.0 to 72.8 GyE)

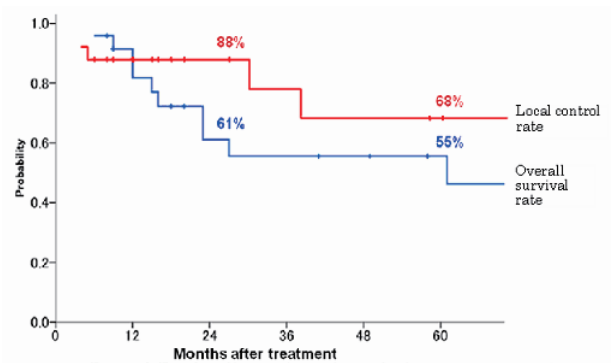

Figure 2. Results of heavy charged particle therapy in patients with cervical adenocarcinoma (n = 24; stage: IIIb to IVa; dose: 68.0 to 74.4 GyE)

4. Conclusion

We have conducted multiple clinical studies on carbon ion radiotherapy in patients with locally advanced cervical cancer, in order to improve the therapeutic outcome. These studies produced excellent results, suggesting that this treatment may be safe and effective for locally advanced cervical cancers that are poorly controlled by conventional approaches (i.e., surgery and chemoradiotherapy).

Carbon Ion Radiotherapy for Pancreatic Cancer

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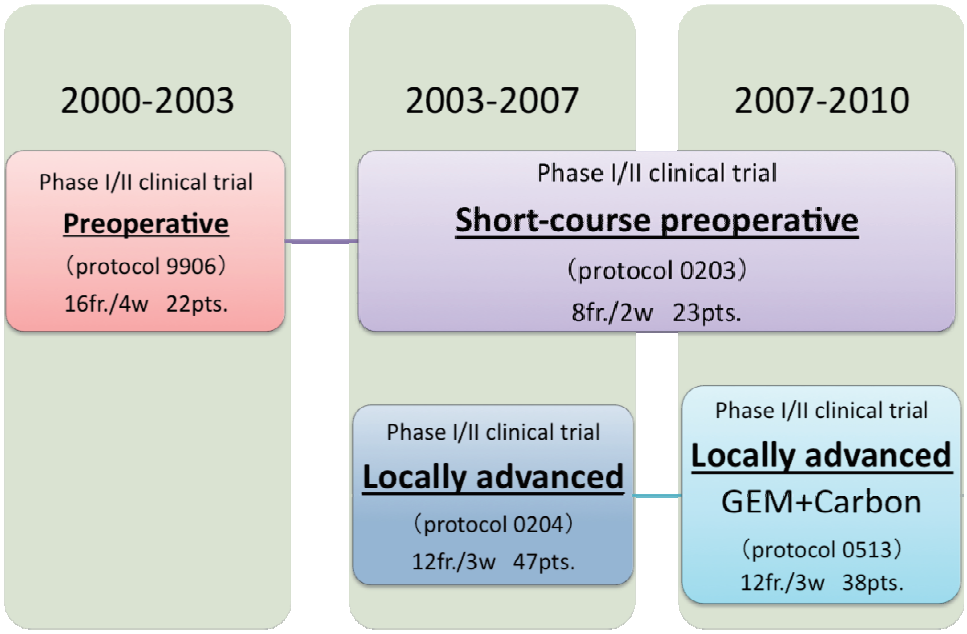
<Background>

The number of deaths from pancreatic cancer in Japan exceeds 20,000 per year, and the number is increasing every year[1]. Pancreatic cancer is the fifth leading cause of cancer death and it is considered to be one of the most lethal cancers. Complete surgical resection is the only curative treatment. However, only a small percentage of patients (10-20%) are candidates for surgical resection because of local progression or metastatic spread at the time of diagnosis[2, 3]. Even if a curative resection is performed, the disease usually recurs, and 5-year survival rates are less than 20% [4, 5].

Chemotherapy or chemoradiotherapy is selected as a standard treatment for unresectable pancreatic cancer. However, since pancreatic cancer is often resistant to chemotherapy or radiotherapy, the local control rate is very low. Recently, along with the development of new anticancer agents, the irradiation techniques have greatly progressed following the introduction of highly advanced radiotherapy. However, the outcome from therapy is still not satisfactory, with the median survival being approximately 10 months[6, 7]. We started phase I/II clinical trial for pre-operative carbon ion radiotherapy (CIRT) with 16 fractions in 4 weeks for resectable pancreatic cancer in 2000 (Figure 1). The purpose of this treatment was to reduce the risk of postoperative local recurrence, which accounts for approximately 50% of total recurrences. We established the tolerance and effectiveness of preoperative CIRT and performed a clinical trial aimed at shortening the fraction size to 8 fractions in 2 weeks beginning in 2003 (Protocol 0203). In addition, we started phase I/II clinical trial for patients with locally advanced pancreatic cancer and showed that the treatment was safe and provided excellent local control rates. Accordingly, we are currently performing a clinical trial of using carbon ion radiotherapy combined with gemcitabine (anticancer agent) (Protocol 0513).

Figure 1. The clinical trial pathway of carbon ion radiotherapy against pancreatic cancer.



I. Preoperative carbon ion radiotherapy for patients with resectable pancreatic cancer (Protocol 0203)

<Objective>

The purpose of this study was to evaluate the tolerance and efficacy of CIRT as preoperative irradiation, and to determine the recommended dose needed to reduce the risk of postoperative local recurrence without excess injury to normal tissue.

<Materials and methods>

The eligibility criteria for this study were: that the pancreatic cancer was judged to be radically resectable without involvement of the celiac trunk or superior mesenteric artery. We performed CIRT with 8 fractions in 2 weeks, and resection 2-4 weeks after the irradiation. We started irradiation at a dose of 30GyE/8 fractions, fixed the irradiation fractions and increased the radiation dose by 5% increments.

<Results>

Twenty-three patients were registered from April 2003 through February 2010, and dose escalation was performed from 30GyE to 36.8yE. We have administered CIRT to all patients as scheduled. The clinical stage according to the UICC was stage IIA in 15 cases and stage IIB in 8 cases. Nineteen out of 23 patients received curative resection (resection rate 83%), however, the remaining 4 patients did not undergo surgery due to liver metastases or because they rejected the surgery. Only one patient developed acute grade 3 toxicity, which was a liver abscess due to chemotherapy for liver

metastases. No other serious adverse effects were observed. In the 19 surgical cases, the 3-year local control rates and overall survival rates were 100% and 40%, respectively.

II. Gemcitabine combined with carbon-ion radiotherapy for patients with locally advanced pancreatic cancer (Protocol 0513)

<Objective>

The purpose of this trial was to establish the recommended dose of gemcitabine and CIRT, evaluating the tolerance and efficacy of gemcitabine, which is a standard anti-cancer agent for advanced pancreatic cancer, combined with CIRT.

<Materials and methods>

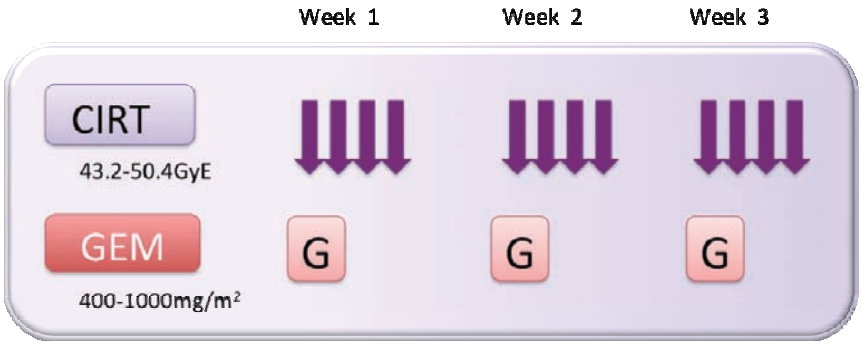
The eligibility criteria for this study were: locally advanced pancreatic cancer which involved the celiac trunk or superior mesenteric artery without distant metastasis. All patients had histologically- or cytologically-proven pancreatic adenocarcinoma or adenosquamous carcionoma. The radiation fractions were fixed at 12 fractions in 3 weeks, and the dose of gemcitabine and radiation were gradually increased. First, the dose was fixed at 43.2GyE/8 fractions and the gemcitabine dose was increased from 400, to 700 to 1000mg/m^2. Subsequently, the gemcitabine dose was fixed at 1000mg/m^2 and the radiation dose was increased by 5% increments (Figure 2). Gemcitabine was administered for 3 consecutive weeks, once a week (Figure 3). The irradiation field was set in the range that included the primary tumor, perineural lesions and prophylactic regional lymph node area.

Figure 2. The dose enhancement trial (Protocol 0513)

CIRT*	GEM**
43.2GyE	400mg/m^2 ↓ 700mg/m^2 ↓ 1000mg/m^2
45.6GyE ↓ 48.0GyE	1000mg/m^2 / 1000mg/m^2

CIRT*: Carbon Ion Radiotherapy, GEM**: gemcitabine

Figure 3. Treatment schedule (Protocol 0513)



<Result>

Thirty-eight patients were registered from April 2007 through February 2010. Their clinical stage according to the UICC was stage III in 34 cases and stage IV in 4 cases. Dose limiting toxicity (DLT) developed as an early adverse event in 3 out of 38 patients, which was a low incidence. No other serious side effects, including late adverse effects, were found. The combinations with full-dose gemcitabine (1000mg/m2) did not show any increased incidence of adverse effects with dose escalation. Local control by CIRT increased along with the dose escalation. In the high dose group, in which patients were irradiated with at least 45GyE, local recurrence developed in only one out of the 14 patients. The one year local control rate was 86%. The median survival was 18 months, and the 1-year and 2-year overall survival rates were 66% and 34%, respectively.

<Conclusion>

Preoperative CIRT can be performed safely without serious side effects and was proven to be useful as a method to reduce the risk of postoperative local recurrence. Hereafter, accumulate cases and further discussions about the curative effect are necessary.

Furthermore, CIRT was also well tolerable even when concomitantly administered with the highest dose of gemcitabine (1000mg/m^2). Long-term survival or radical cure can be expected by performing further dose escalation or maintenance chemotherapy.

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What's Next in Carbon Ion Radiotherapy at NIRS?

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Summary

Since its launch by the National Institute of Radiological Sciences (NIRS) in 1994, cancer therapy using heavy ion beams (carbon ion beams) has been used in approximately 5,500 patients. Accumulated clinical experience has identified certain types of malignant tumors that respond exclusively to this treatment. It has also been made clear that this therapy is capable of treating several other types of cancers safely in a relatively short period of time, effecting remission and/or cure without pain or discomfort in a few days or weeks. We can reasonably state that heavy ion radiotherapy has been established as a safe and effective treatment method. NIRS researchers are continuing to make every effort to develop more effective, efficient, and patient-friendly heavy ion irradiation systems. The result of this research and development is also expected to slash the attendant costs of heavy ion radiotherapy.

Current Heavy Ion Radiotherapy

Japan is the front-runner in heavy ion radiotherapy, which so far has shown to be superior to conventional radiation therapy in terms of both dose localization (spatial dose distribution) and anti-tumor effect (cytocidal effect). Owing to these properties, heavy ion radiotherapy provides a safer, faster, and more definitive result than conventional approaches. High-velocity acceleration (approximately 80% of the speed of light) of the heavy ions (carbon nuclei) is necessary to penetrate the human body. Until recently, this required a huge facility. NIRS's original HIMAC (Heavy Ion Medical Accelerator in Chiba) facility, with its 42-m diameter synchrotron rings, required approximately 33 billion yen for its construction. NIRS has now developed a new, smaller accelerator that is equivalent in performance and capacity to the current HIMAC facility, at a cost of one-third of the original. A demonstration accelerator was installed at Gunma University, Japan, and has been in operation since March 2010.

At present, five heavy ion treatment facilities are operating around the world; three of them are located in Japan. Construction of two more small-scale facilities has been approved in Japan (Saga and Kanagawa Prefectures). Overseas, around a dozen facilities are being planned or implemented in the following countries: Germany (two sites under construction), France, Italy (facility undergoing trial operation), Austria, China, South Korea, Malaysia, Saudi Arabia, and USA (Mayo Clinic).

European and American manufacturers hold the majority share of the world's advanced medical equipment and devices market. However, as far as heavy ion radiotherapy is concerned, Japan enjoys a superior position in competitiveness with respect to equipment manufacturing techniques and clinical experience. Of 7000 patients treated with heavy ion radiotherapy worldwide, more than 80% were treated at the NIRS and other locations in Japan. Japan has the potential to continue to be the world leader in this field.

Next-generation Heavy Ion Radiotherapy

Clinical experience has demonstrated the superiority of heavy ion radiotherapy over other radiation modalities for the treatment of various types of tumors. The current facilities and devices may be termed as first-generation equipment. As with other novel modalities such as MRI and PET, it is important for manufacturers to always be working on the next generation of a device, both to improve patient care and to bolster international competitiveness in a rapidly growing market. Mere downsizing of equipment is being far from satisfactory in this market.

One new technique that deserves attention is the spot scanning irradiation method, which superimposes multiple "pencil" beams of heavy ions to cover a target area. The NIRS has also been working on a respiratory-gating technique, the world's first application of a gating method to this modality. NIRS has finished the construction of the new facility's building, and is in the process of installing the equipment. The new treatment facility will be comprised of two therapy rooms, each with a roboticallly-controlled patient table and fixed horizontal and vertical spot scanning irradiation ports. Another innovation, a rotating gantry will provide more degrees of freedom in beam direction.

1) Spot Scanning Irradiation and Rotating Gantry

Spot scanning irradiation is designed to treat the complex-shaped lesions that are difficult targets for the by current techniques. It will adjust to the change in tumor size over time (intensity modulated and adapted

carbon ion radiotherapy). The current treatment procedure for prostate cancer requires 12 to 16 fractions over 3 to 4 weeks. The number of fractions can potentially be shortened by applying this new technique, as it can reduce the exposure to the prostatic urethra. Use of the rotating gantry will minimize the time for patient positioning and improve patient comfort. For example, in the case of a patient with lung cancer, the current system requires 1.0 to 1.5 hours per session. The new system will reduce it to 30 minutes, because the operator may irradiate the patient as many times as necessary from any desired direction, after only one determination of lesion location. Owing to simplified treatment set-up procedures and reduced treatment time, more patients with poor clinical status will be eligible for this therapy. We anticipate that the introduction of these innovations will not only improve the therapeutic outcome but also increase patient throughput. In the early period of carbon ion therapy at NIRS, patients with prostate cancer received 20 fractions over 5 weeks. The regimen was later replaced with a 16-fraction 4-week protocol. As a result, the number of patients treated per year increased from 100 to 150. At present, a course of 16 fractions is the standard procedure for the treatment of prostate cancer, and some 200 patients are being treated annually. Simple calculation indicates that about 400 patients can be treated per year by reducing the number of necessary fractions to eight. The new system will also eliminate the need for constructing compensation filters as well as patient-specific collimators. Apart from the cost for construction of the facility and the labor cost of personnel engaged in its operation, the anticipated sparing of expenses for compensation filters and collimators and the increase in the number of patient slots will reduce the cost of the therapy.

We have begun to explore the possibility of applying superconductivity technology to carbon ion radiotherapy for the next generation of radiotherapy system. The author wishes to launch an innovative system, which could be installed and operated for a reasonable cost, and marketed widely for a large number of indications. This will represent one step in the movement to revitalize the once-vibrant Japanese economy and can help Japan regain its leadership position in cutting-edge medical technology. The author also desires to train and equip professionals who will take the lead in advancement of the field of heavy ion radiotherapy.

Summary

Some of the major short-term goals for research and development in the field of heavy ion radiotherapy for cancer are to:

1) Establish standard treatment procedures (e.g., indications, protocol, operating procedures, facility standards, quality assurance and quality control)
2) Improve treatment efficiency (e.g., use of spot scanning and rotating gantry, development of short-term outpatient irradiation program)
3) Conduct new clinical trials to treat refractory tumors, develop new therapeutic approaches, compare with other methods, evaluate the efficacy of concurrent therapy, and possibly widen the indications for the therapy
4) Investigate new irradiation techniques (e.g., respiration gated spot scanning irradiation)
5) Develop ultra small-sized superconductivity-based rotating gantry and accelerators

Achievement of these goals will lead to the establishment of 'global standards for heavy ion radiotherapy' that will have a strong impact on the following:

1) Maximization of the medical benefits accruing to society from research (widening of the national health insurance coverage)
2) Training and education of professionals in heavy ion radiotherapy.
3) Efficient use of available resources and facilities

Overview of the Proton / Carbon Ions Facilities in Europe.

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Over 60.000 patients have been treated world wide with protontherapy and there is no doubt that proton based irradiation can achieve in many clinical circumstances similar tumor dose distributions compared to the most up to date X-rays delivery but can also avoid unnecessary irradiation of normal tissues and reduce the integral radiation dose. This is well in line with the European ALARA principle (irradiation as low as reasonably achievable). Despite of the ballistics advantages of the protons and the promising clinical results, the development of protontherapy and its use in Europe have been very restricted so far, probably due what is considered as the need for heavy and costly structures to produce proton beams. About 800 000 patients are being treated every year with radiation therapy throughout Europe and only a very small proportion of them are having access to protontherapy with number of patients still below 2-3000 / year treated in less than 10 centers, which overall is less than 0.3% of all the patients treated with radiation.

A numerous of additional projects are being developed, either to promote machines with a dual capability to accelerate both protons and carbon ions (Heidelberg, CNAO, Archade etc…) or new types of compact machines for proton acceleration (Nice).

Given the existing capacities for treating patients with protons in Europe, the clinical indications are extremely limited and restricted to well established tumor sites and histology (eye melanoma, base of skull and pediatric tumors …). Despite European academic networks very active in the field (Enlight, Ulice…), it is currently very difficult to set up and realise in Europe the needed randomized clinical trials that would generate EBM level 1 to demonstrate that this form of treatment has a real clinical added value for improving the results of radiotherapy (especially in relation to reducing treatment related side effects) and its contribution to the overall control of cancer. EBM level 1 is being generated outside Europe (ex : at MDACC for lung cancer …) and will should markedly contribute to speed up the whole process of expansion of proton therapy, which at some point will be inevitable but at the moment which is slowed down by the absence of EBM level 1.

KIRAMS project: New Challenges from CyberKnife to Heavy Ion Radiotherapy

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Abstract

Korea Institute of Radiological and Medical Sciences began its history of radiotherapy with Co-60 teletherapy, and made a consistent effort for the development and introduction of new technologies and equipments to fulfill our mission, “to contribute to public health through the medical applications of radiation and biotechnology.” KIRAMS is familiar to become the first. KRIAMS was the first organization that operated CyberKnife and PET-CT in Korea as well as Cobalt treatment equipment. Today, we begin our new challenges to Heavy Ion Radiotherapy.

Korea Institute of Radiological and Medical Sciences

Korea Institutes of Radiological and Medical Sciences, KIRAMS, an institution specializing in radiation and health, is a medical complex composed of the Radiological and Medical Sciences Research Center, the Korea Cancer Center Hospital, and the National Radiation Emergency Medical Center. Radiological and Medical Sciences Research Center dedicated to comprehensive radiation medicine research across a broad span of basic science to clinical application. Korean Cancer Center Hospital (KCCH), which has 40 years of history, has been a pioneer in developing and applying cancer diagnosis and treatment technologies. National Radiation Emergency Medical Center (NREMC) develops a national network system in preparation for possible radiation emergencies.

Dongnam Institute of Radiological and Medical Sciences

In addition to our facilities in Seoul, Korea, KIRAMS opened Dongnam Institute of Radiological and Medical Sciences (DIRAMS) at BUSAN in 2010. DIRAMS is aimed to enhance health care delivery for the residents of the southeast region where over two third of nuclear power plants are in operation.

DIRAMS is the medical hub equipped with experienced professional medical staff and the cutting-edge treatment equipments such as CyberKnife, PET-CT, IMRT, and also the research hub of the region leading academia-industry collaboration.

CyberKnife

A new chapter in radiotherapy history of KIRAMS began with the operation of the first Co-60 teletherapy (cobalt treatment equipment) in Korea back in 1963. Over the years, KIRAMS introduced and operated state of the art radiotherapy to provide the best treatment for cancer patients.

With the nation’s first operation using the CyberKnife technology in 2002, the CyberKnife Center opened the era of ‘a no bleeding cancer operation.’ The CyberKnife Center treats brain tumors, brain vessel diseases, tertiary neuralgia, Parkinson’s disease, and epilepsy. It also treats the diseases such as spine oncology, spine vessel

diseases, lung cancer, liver cancer, pancreas cancer, prostate cancer, etc, which were not treatable with conventional radiation treatment equipment. CyberKnife Center reached up to one thousand successful treatment cases recently.

Korea Heavy Ion Medical Accelerator Project

KIRAMS has been playing a leading role in cancer treatment and research on the medical and biological applications of radiation and radioisotopes for the last 40 years and in 2010, KIRAMS launched Korea Heavy Ion Medical Accelerator Project, KHIMA project, to develop and construct the heavy ion medical accelerator for the first time in Korea. The term of KHIMA project is from April 2010 to March 2016. By 2016, we plan to build the heavy ion treatment center in Busan, which is close by Busan branch of KIRAMS and start the treatment.

KIRAMS will take a leading role in heavy ion accelerator development including Heavy Ion Accelerator (Carbon-400MeV/u) and Treatment System. Thus we consider the establishment of a domestic consortium and the collaborative development with foreign institute. For treatment system including patient tracking system and treatment planning system, KIRAMS has plan for a collaborative development with foreign institute.

From the experiences in developing Cyclotron 13 MeV and 30 MeV, KIRAMS possess the technology and high skilled manpower to develop the accelerator. Now, KIRAMS is ready to create a new history of radiotherapy with development of Korea Heavy Ion Medical Accelerator.

Mayo Clinic Charged Particle Cancer Treatment Program

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William Worrall Mayo moved to Rochester, Minnesota in 1864 to serve as a physician for the Union Army during the Civil War. His two sons, William J. Mayo and Charles H. Mayo followed in their father's footsteps and became physicians and surgeons. Together, they ultimately founded what has become known as the Mayo Clinic.

This year the Mayo Clinic is celebrating the 100 year anniversary of a famous speech delivered by Dr. William J. Mayo during the commencement program of the Rush Medical College in Chicago, Illinois. During his speech, Dr. Will stated, "The best interest of the patient is the only interest to be considered." This idea served as the basis for the primary value of the Mayo Clinic, "the needs of the patient come first." The mission of the Mayo Clinic is "to inspire hope and contribute to health and well-being by providing the best care to every patient through integrated clinical practice, education and research."

Mayo Clinic was the first and has become the largest integrated, not-for-profit group medical practice in the world with over 3700 physicians and scientists representing every medical and surgical specialty. Overall 49,000 allied health staff helps the physicians to care for over 500,000 patients each year. The Mayo Clinic is led by physicians coupled with administrative partners and is governed by a Board of Trustees with 29 members including representatives from the public and from the Mayo Clinic physician and administrative staff. As a not-for-profit foundation, all income from the clinical practice is reinvested into the practice, in addition to funding education and research programs. Mayo Clinic's commitment to education and research is manifested by it's investment of $769,000,000.00 USD in its education and research programs in 2009.

The education programs at Mayo Clinic include 5 schools, the Mayo School of Graduate Medical Education, the Mayo Graduate School, the Mayo Medical School, the Mayo School of Health Sciences and the Mayo School for Continuous Professional Development. The Mayo School of Graduate Medical Education was established in 1915 and currently consists of more than 250 residency and fellowship programs (including radiation oncology residency and fellowship programs and a medical physics residency program) with nearly 1500 residents and fellows enrolled each year, nearly 600 graduates each year and over 19,000 alumni throughout the world. The Mayo Graduate School was established in 1917 and began granting independent MS and Ph.D. degrees in 1989 after working for many years with the University of Minnesota. Currently there are more than 10 biomedical subspecialty programs with 271 students enrolled. There are approximately 48 graduates each year with over 700 alumni worldwide. The Mayo Medical School was established in 1972. Currently, 169 students are enrolled and 38 graduate each year with over 1475 alumni throughout the world. Since the very early years of the Mayo Clinic, physicians from around the world have traveled to Rochester for continuing medical education activities. The Mayo School of Continuous Professional Development was more formally established in 1996 as the Mayo School of Continuing Medical Education and currently

provides about 283 courses per year comprised of over 10,000 hours of instruction for over 120,000 participants. Finally, many of the allied health staff employed at Mayo Clinic are trained within the Mayo School of Health Sciences which was formally established in 1973 and has 123 allied health science programs (including radiation therapy technologist and certified medical dosimetrist) with about 1400 students enrolled and over 900 graduates each year. There are nearly 12,000 alumni.

Mayo Clinic is actively engaged at all levels of research including basic science, translational and clinical. Mayo Clinic is one of the top 20 NIH funded academic medical centers with 394 awards from 27 institutes in 2009. There are over 3200 physicians and scientists engaged in research with over 2800 grants and contracts and over 800,000 square feet of research space. There were over 4600 peer-reviewed citations in 2009. There were over 2500 new human studies approved in 2009 bringing the total to over 7700 active human studies. Mayo Clinic has been an NCI designated comprehensive cancer center since 1973. There are currently 450 physicians and scientists who are members of the Mayo Clinic Cancer Center with over $210,000,000.00 USD in funding.

Over the years, the Mayo Clinic has earned a world-renowned reputation for the diagnosis and treatment of complex and difficult diseases. Virtually all subspecialties of medicine and surgery are represented within a single institution. This breadth and depth of staff and facilities allows for diagnosis and treatment within just a few days.

The Mayo Clinic has 3 large group practice locations in Phoenix and Scottsdale, Arizona; Jacksonville, Florida and Rochester, Minnesota. In addition, the Mayo Clinic Health System is a group of 17 hospitals and 70 clinics in Minnesota, Iowa and Wisconsin that comprise a community-based healthcare network. Over 20,000 patients with cancer are seen within the Mayo Clinic system each year. We evaluated over 3500 patients that were treated with radiation therapy in 2009 in Rochester, Minnesota or at one our 4 regional practice sites in Minnesota and Wisconsin. We found that over 1500 patients had indications for and may have benefited from proton beam therapy. In addition, there were another nearly 800 patients that were seen in Rochester but elected to have their radiation therapy performed elsewhere who also had indications for and my have benefited from proton beam therapy. Using a combination of census data, cancer incidence rates, and radiation therapy utilization rates by geographic location and projecting the population growth to the year 2015, we estimated that there are 2400 patients living within 120 miles of Rochester, Minnesota that could benefit from proton beam therapy and another 20,000 patients living within 500 miles of Rochester, Minnesota. We estimated that there would be 2500-3000 patients living in Arizona that could benefit from proton beam therapy with another 4370 patients living within the adjoining states of New Mexico, Colorado and Nevada. A conservative estimate is that there are approximately 137,000 patients in the US each year that may benefit from proton beam therapy. The current treatment capacity is only 11,000 patients per year. The demand for proton beam therapy is greater than the current treatment capacity in the US.

We believe that proton beam therapy is consistent with the primary value and mission of the Mayo Clinic; it is in the best interest of the patient. We believe that proton beam therapy holds promise for improving tumor control and prolonging survival by increasing the dose to the tumor. Similarly, particularly for “radiation resistant” cancers or recurrent previously irradiated cancers, heavier charged particles, such as carbon ions, may improve tumor control and survival because of a greater biological effectiveness when compared to protons or x-rays. This should reduce the cost associated with treating recurrent cancer. We believe that there is potential for fewer severe acute and late side effects and complications with proton and carbon ion therapy due to the physical advantage of the Bragg-Peak (more accurate and precise targeted delivery of the radiation

dose) with a lower dose of radiation administered to critical normal organs and tissues surrounding the cancer target. This is particularly important for young children, adolescents and young adults who have curable cancers and suffer greatly from the late effects of x-ray therapy on normal organs. Charged particle therapy should reduce the costs associated with treating acute and late side effects of conventional x-ray radiation therapy. Finally, with proton and carbon ion therapy, there is an opportunity to reduce the number of treatments by at least 50%, if not more, compared to x-ray therapy. This would be beneficial to the patient in reducing out of pocket expenses for travel, food and housing while receiving radiation therapy. It would also reduce the burdens on family members and friends who take time off work to accompany the patient for treatment and to care for them. It may also reduce the amount of time off work for the patient and relieve the emotional suffering associated with a prolonged course of cancer treatment.

We believe that about 30% of our current practice in Rochester, Minnesota may benefit from lowering the dose to normal organs with the use of proton beam therapy. Some examples include lowering the dose to the bladder, small bowel and hips in the case of gynecologic cancers (such as vaginal, vulvar, cervical and endometrial cancers), and gastrointestinal cancers (such as anal and rectal cancers). Another example is lowering the dose to the heart, lung, and esophagus in the case of breast cancer, lung cancer, gastric cancer, esophageal cancer and lymphomas, especially Hodgkin's Lymphoma in children and young adults. All pediatric patients should benefit from the lower dose to normal organs associated with proton beam therapy in light of their developing organs, high likelihood of prolonged survival and risk for radiation-induced malignancies. A young adult with lymphoma or breast cancer would also have a lower risk of developing a radiation-induced malignancy later in life.

Another approximately 30% of our current practice in Rochester, Minnesota may benefit from the greater biologic effectiveness of heavier charged particles such as carbon ions in addition to the positive effects of lowering the dose to the normal organs surrounding the cancer. Examples include inoperable "radiation resistant" salivary, thyroid and sinus cancers (particularly melanoma). Additional examples include cervical, hepatobiliary, pancreatic, and lung cancers and soft tissue or bone sarcomas. Patients with lethal prostate cancer (high PSA, high Gleason score, advanced T-classification) may benefit from a hypofractionated course of proton or carbon ion therapy combined with androgen deprivation therapy. Proton beam and carbon ion therapy may have a role in patients with inoperable previously irradiated cancers.

Two of the main concerns about proton and carbon ion therapy are the cost and the lack of evidence of safety, efficacy and cost effectiveness when compared to conventional cancer treatments. This creates opportunities for clinical research. These opportunities include, but are not limited to, phase I clinical trials to determine the safety and maximally tolerated dose of proton beam or other charged particles either alone or combined with chemotherapy or biologically targeted agents for a wide variety of cancer types (radiation sensitive and radiation resistant cancers). Phase II clinical trials also need to be performed to determine the efficacy (tumor control and survival) of protons and other charged particles either alone or combined with chemotherapy or biologically targeted agents for a wide variety of cancer types. These studies could include determining the optimal fractionation schedule with which to administer the treatment perhaps leading to reduced costs and improved convenience by reducing the number of treatments to a minimum. Phase III clinical trials could be developed to evaluate and compare tumor control, toxicity, function, quality of life, convenience, survival and cost effectiveness associated with protons or other charged particles and conventional x-ray treatments either alone or combined with chemotherapy or biologically targeted agents.

There would also be opportunities for basic science research to understand the molecular and cellular mechanisms associated with DNA repair and cell death associated with charged particle therapy.

We can see the potential in the future for individualizing radiation therapy, choosing from an array of options including x-rays, protons or one of several heavier charged particles based on age, gender, cancer type, anatomic location and genetic profile of the cancer and/or the patient's normal tissues ("radiogenomics").

Additional research opportunities include the evaluation of charged particles in the treatment of benign disease, the physics of treatment delivery and verification, radiation protection during space travel and radiation hardening of integrated circuits.

Charged particle therapy also is associated with several educational opportunities including development of training programs for radiation oncology medical residents and fellows, visiting physicians, medical physics residents and fellows, radiation therapists and certified medical dosimetrists.

Our plan is to integrate charged particle therapy into our department of radiation oncology and our oncology practice as an additional cancer treatment modality. Our cancer treatment program will be composed of three phases. Phase I will begin with two proton beam treatment facilities, one in Phoenix, Arizona and the other in Rochester, Minnesota. These facilities will have gantries and pencil beam scanning. Phase II will be a facility with helium and carbon ion beams for clinical use. We are planning on having two treatment rooms with dual fixed beams and pencil beam scanning. There will be a research room in addition. Finally, phase III will consist of a wide range of charged particle research beams for basic biology and physics research. Lithium, Beryllium, Oxygen and Neon beams will be used for biologic and human studies. Iron, Krypton and Xenon beams will be used to study space radiation effects (physics research).

Phase I will consist of 4 pencil beam scanning gantries in Minnesota and Arizona (8 treatment rooms total) capable of treating >2400 patients per year. There will be 2 fixed beam rooms for research purposes. Building design will commence in 2011. Permission has been granted to develop a business plan for phase II and III.

Based on currently operational proton beam facilities, we estimated that on average, it will take 26 minutes to treat each patient which would be 2.3 patients treated per hour. We plan on operating 15 hours per day with two shifts. Our facilities will be open 242 days per year for a total of 8350 treatments per room per year. We have estimated that on average each patient will receive 27 treatments which would result in 310 patients treated per year per room for a total of 2480 patients per year and 276 patients per day (8 treatment rooms). Each facility will open with two treatment rooms operational with the third and fourth treatment rooms coming online 6 and 12 months later. We estimated conservatively that it will take approximately 5 years to fill the treatment rooms to full capacity. When fully operational, we estimate that each facility will be staffed by 129 to 136 FTE including 19 to 22 physicians and physicists and 110 to 114 allied health staff. The staff will be composed of radiation oncologists, physicists, radiologists, anesthesiologists, nurse practitioners, physician assistants, dosimetrists, beam shaping technicians, radiation therapists, immobilization technicians, registered nurses, social workers, dieticians, programmers, business representatives, medical secretaries, transcriptionists, administrative assistants, calendar coordinators, clinical assistants, receptionists, patient appointment coordinators, treatment schedulers, nurse abstractors, protocol development coordinators, data managers, radiology technologists, special imaging assistants, certified registered nurse anesthetists, operations managers, facility maintenance workers, environmental services workers, security, general services workers and clinical engineers.

The current estimate for our project schedule is design of the proton beam facilities during 2011; develop a business plan for heavy charged particles during 2011 and 2012; building construction during 2011-2013; equipment design, manufacture and installation during 2011-2014, equipment and beam testing during 2013-2015; first patient treatment in late 2014 and all rooms available for patient treatments in 2016.

Prefectural Plan to Install a Heavy Charged Particle Radiotherapy System at Kanagawa Cancer Center: A Progress Report

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Introduction

In Japan, heavy charged particle (carbon ion) radiotherapy was pioneered by the National Institute of Radiological Sciences (NIRS), which started to treat cancer patients using this new technique in June of 1994. Around 750 patients seeking treatment visit this hospital every year.[1] Based on their experience, the Hyogo Ion Beam Medical Center (HIBMC)[2] and Gunma University Heavy Ion Medical Center (GHMC) subsequently started using carbon ion therapy. Saga Prefecture is ardently promoting a local community-based project to build the SAGA Heavy Ion Medical Accelerator in Tosu (HIMAT). Kanagawa Cancer Center (KCC) is also pursuing plans to introduce a heavy charged particle (carbon ion) radiotherapy system and start its operation in 2015.

Basic Conceptual Framework

The basic principles of the carbon ion radiotherapy system to be installed in the KCC are to: provide patient-friendly medical care that improves quality of life, and to build up the capacity to fulfill its medical care, research, and teaching mandates (Figure 1). The forthcoming planned carbon ion radiotherapy system is expected to provide many patients with advanced therapy tailored to clinical practice.

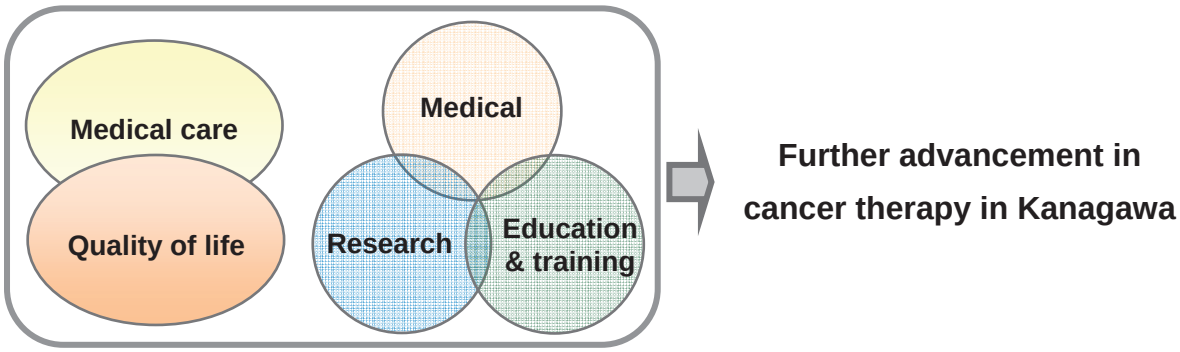

Figure 1. Basic Conceptual Framework of the Carbon Ion Radiotherapy System.

Characteristics of the Forthcoming Radiotherapy Facility

The KCC is located in Yokohama, Kanagawa. The location of this center benefits from an excellent and efficient public transportation network covering the entire area of Kanagawa Prefecture and extending into the

southern and western parts of Tokyo Metropolitan District. The KCC stands at an ideal location for receiving outpatients from local, regional, and even distant areas. One of the major missions of the forthcoming radiotherapy facility is to provide the latest medical treatment in an outpatient setting.

This facility will be managed and operated in close cooperation and coordination with other department in the KCC, with the help of its cancer specialist surgeons, who will design high-level medical treatment for various types of cancer. The combination of this facility's carbon ion radiotherapy system 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.

In addition to conventional irradiation techniques (the wobbler method), a spot scanning irradiation method will be included in the treatment options from the start of the facility operation. The combination allows a wider selection of irradiation methods depending on patient conditions.

- **Outpatient treatment facility**
- **Close cooperation with other departments in the KCC**
- **Full-range services of a radiation oncology center**
- **Initiative to adopt the spot scanning irradiation technique**

Figure 2. Characteristics of the Carbon Ion Radiotherapy Center in the KCC

Outline of the Facility

The carbon ion radiotherapy facility will be established in conjunction with the planned permanent relocation of the hospital ward. Discussion on the project to build a heavy particle radiotherapy facility started in 2004. The basic framework and design of the new facility were completed in early 2010. In and after 2011, the facility building and therapy equipment will be designed and constructed; various data necessary for performing the radiotherapy will be collected. After trial operation of the treatment system and regulatory approval of the medical devices, the facility will be open to the public.

The carbon ion radiotherapy facility will be built adjacent to the hospital building (Figure 3). This three-story building will have one ground floor and two underground floors. The lowest floor will house the treatment rooms. On the same underground level of the main hospital building will be located high-precision radiotherapy equipment: four units of photon radiotherapy equipment (x-ray and electron beams [the number will be increased to 5 in the relatively near future]) and one brachytherapy device. The first underground floor of the carbon ion radiotherapy facility will house the power supply for the medical equipment. The ground floor will include various rooms for treatment planning, conferences, lectures, meetings, utilities, as well as the power supply for air-conditioning and other energy demands.

Figure 3. Illustration of the new Kanagawa Cancer Center (Left figure: General view of the KCC, Right figure: the hospital building)

The irradiation system will be modeled after the 'common-grade' carbon ion radiotherapy system developed by the NIRS.[3] The ion source, injector (linear accelerator), main accelerator (synchrotron), and the beam transport system will be similar to the common-grade version. The facility will have four treatment rooms, consisting of three for wobbler irradiation and one for spot beam scanning irradiation (Table 1).

Table 1. Provisional Outline of Heavy Ion Facility (KCC)*

Component	Description
Ion Species	Carbon ion
Maximum accelerated energy	400 MeV/n
No. of treatment rooms	4 (2 with horizontal ports and 2 with horizontal & vertical ports)
Irradiation method	Wobbler and spot beam scanning
Patient positioning	x-ray radiography and CT simulation

**The details may be subject to change.*

Target Number of Patients

Table 2 presents the estimates of the numbers of eligible patients residing in Kanagawa to whom carbon ion radiotherapy would be applicable. We used these estimates to predict the total annual number of treatments and design the medical facility. At present, the carbon ion radiotherapy center is expected to treat 880 patients a year at its full capacity.

Table 2. Estimations of the Annual Number of Patients to be Treated in Kanagawa

Tumor site	No. of patients	Tumor site	No. of patients
Lip	63	Rectum and anus	268
Tongue		Liver and intrahepatic duct	265
Gingiva		Spleen	11
Floor of mouth		Nasal cavity/auris media/nasal sinus	58
Palate		trachea/bronchus/lung	581
Other and mouth unspecified		Bone and articular cartilage	9
Parotid gland	18	Connective tissue/soft tissue	21
Major salivary gland	12	Cervix (invasive tumor)	7
Tonsil	63	Uterine body	1
Oropharynx		Prostate	890
Nasopharynx		Kidney (excluding renal pelvis)	3
Pyriform sinus		Bladder	58
Hypopharynx		Eye	9
Oral cavity/pharynx unspecified		Brain	15
Esophagus	53	Other/nervous system unspecified	
Colon	38	Thyroid gland	3
Total			2,446

The figures were estimated from the numbers of patients with tumors living in Kanagawa by the National Institute of Radiological Sciences, which were taken from the *Kanagawa Malignant Neoplasm Registry 31st Report (March 2008).*

Conclusion

The master plans and fundamental design studies for the carbon ion radiotherapy facility were established in early 2010. Detailed designs for the facility building and the radiotherapy system are now being discussed in light of ongoing technological progress. The new facility will take the initiative to adopt the spot scanning irradiation method. This state-of-the-art facility will start its operation in 2015.

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Future Plan of Heavy Ion Radiotherapy in Taiwan

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Introduction

Cancer has been the leading cause of death in Taiwan for the past decades. Like proton therapy, carbon ion therapy uses charged particles to deliver more precise, localized radiation to tumors with less exposure to surrounding tissues than x-rays. But unlike proton therapy, carbon ion therapy causes damage to cancer cells in a way that they cannot repair themselves. At present, there are two proton therapy facilities under construction in Taiwan - one at Chang-Gung Memorial Hospital and the other one at the National Taiwan University Hospital. In view of the better biological effect than proton therapy, interest in carbon ion therapy is increasing globally, especially in Europe and Asia including Taiwan. Aiming for excellence in cancer treatment and research, Taipei Veterans General Hospital (TVGH) is currently working on introducing the first carbon ion radiotherapy facility in Taiwan. Herein, we summarize the organization and development for this high-tech radiotherapy in our hospital.

Taipei Veterans General Hospital has been long-term as one of the leading modernized general hospital (about 3,000 beds, one of two National medical centers)in medical education, research and clinical service in Taiwan, especially in the field of cancer care. With team works of various specialties, including surgical oncology, medical oncology, radiation oncology, and diagnostic radiology, the outcomes of cancer patients are comparable to other world-class medical centers. One of our mission is to provide the cut-end treatments for our patents. As early as in 1995, we had proposed to establish a particle therapy center in Taiwan. Since then, we started to explore the feasibility and possibility of having particle therapy in our hospital, and to keep close attention to its development in other countries. Meanwhile, our faculties were enabled learning experiences from other well-knowned Medical Center to be capable of executing this project. The cost of particle therapy was the main obstacle at that time. Noting the great potential of carbon ion therapy in cancer care, Mr. Yung-Fa Chang, the President of Chang Yung-Fa Foundation and Evergreen Group announced to invest at least 30 million US dollars in constructing heavy ion radiotherapy cancer center in December 2007. Soon after, Mr. Chang signed memorandum with NIRS to cooperate in introducing this powerful radiotherapy technology into Taiwan. In general with the idea of Mr. Chang try to benefit Taiwanese and/or Chinese cancer patients, we started to approach the possibility of cooperation in the development of carbon ion therapy in May 2009. With his full support about this project, our team members (Superintendent, Vice Superintendent, medical imaging radiologist, radiation oncologist, medical oncologist and medical physicist) in carbon ion therapy had a visit at NIRS/HIMAC discussing the future partnership and site seeing in August 2009. Acknowledging this cooperation will give TVGH ready access to study a unique cancer therapy that has shown great promise in Japanese clinical trials and to benefit our patients. In September 2009 Taipei Veterans General Hospital, made a consensus meeting to confirm the establishment of this promising facility as our priority. Later in December, Professor

Tsujii from NIRS/HIMAC leaded his team members to have a great seminar at our hospital to share their experiences, as well as a siting evaluation for the predetermined location of carbon ion therapy.

Our team members now actively participate academic meetings/symposiums for particle therapy to have further in-depth training and knowledge expansion, including the PTCOG 49 visited HIMAC and Gumma Carbon Ion fucilities and had a meeting with NIRS/HIMAC in May 2010. We are enthusiastically moving forward with this program because we believe it offers additional, extraorinary and innovative options for cancer patients . Currently, we keep on making every effort to work on this high-tech facility to be installed in the near future.

Future Works

The future works include funding resources, faculty training and recruitment, technical support, cooperation with other academic institutions, etc.

1. Funding resources
   The funding of carbon ion therapy remains the main obstacles in initiation this project. Unlike private institutions, the non-profit mission government public hospitals have restriction and limitation in funding resources. Several approaches are undergoing:
   a. Seeking government's support for carbon ion therapy to solve the regulation, limitation and administration affairs for public hospital.
   b. To explore financial support or cooperation from other large scaled business companies.
   c. To assess the strategy of funding from central government and making it a national-based carbon ion therapy facility.
   d. To evaluate the possibility of B.O.T. (Build, Operation and Transfer) for our carbon ion therapy facility.
2. Faculty training and recruitment
   To select potential candidates, including physicians, medical physicists, radiological scientists, and engineers who are interested in carbon ion therapy to be trained at NIRS/HIMAC in the following years.
3. Technical support
   The main technical support will be definitely from NIRS/HIMAC. Other resources from Chang Yung-Fa Foundation and other heavy industries are necessarily in synchrotron/cyclotron maintenance as well.
4. Cooperation with other academic institutions
   To be a partnership with NIRS/HIMAC will facilitate our hospital to create an international laboratory as a platform for other researchers in Taiwan with expertise in radiation and cancer biology to connect with the knowledge and resources available in Japan. In addition to NIRS/HIMAC, we are seeking potential partners to cooperate with in research, including National Yang-Ming University, National Tsing-Hua University, National Synchrotron center ,National Health Research institutes, and Institute for Nuclear Energy Research, etc.

   We will do all the efforts to solve all the key issues as soon as possible and looking forward to starting this great project at Taiwan before the Summer of 2011.

Future Plan of Heavy Ion Radiotherapy in Malaysia

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Abstract

The recent successful outcome of cancer treatment using carbon ion therapy in many parts of the world, in particular, Japan has prompted Universiti Sains Malaysia to initiate the establishment of a heavy ion therapy facility plan in Malaysia to cater for cancer patients in South-East Asia. The road map ahead for Malaysia is by no means easy. However the recent memorandum between USM and NIRS in Chiba and strong support from important relevant national institutions has created interests amongst some stakeholders in Malaysia to look into the development of heavy ion facility. A number of proposed financial plans, investment ideas, site plans, priorities and the level of acceptance of the novel particle therapy ideas in Malaysia will be discussed.

Introduction

Cancer represents second common cause of death in Malaysia. With approximately 40,000 new cancer patients diagnosed every year, there is a great need to look into better treatment facility such as the 'human friendly' particle therapy using proton or carbon ion. It is 'friendly' because the cancer cells are destroyed while causing lesser damage on vital organs and tissues surrounding the tumor. The most recent status of radiotheraphy in Malaysia has been described elsewhere [1].

The more concrete idea of having a carbon ion therapy facility in Malaysia only started in late 2008 by the Advance Medical and Dental Institute (AMDI) of Universiti Sains Malaysia (USM). It was then followed by a visit to the National Institute of Radiological Sciences (NIRS) in Chiba, Japan in the spring of 2009. Heavy Ion Medical Organization (HIMO) of Japan and A2DX Co. Ltd. of Malaysia [2] played a crucial role in assisting the visit. In October 2009, a National Seminar on Heavy Ion Technology was held in Kuala Lumpur. The key presenters were from the leading authority on carbon ion from NIRS, Chiba and Gunma Heavy Ion Medical Centre (GHMC). The seminar was followed by historic signing of three memoranda of understanding between USM and NIRS, USM and A2DX and between A2DX and HIMO.

To proceed forward with the idea, in April 2010 a dialogue on *Bringing Heavy Ion Therapy in Malaysia* was held in Putrajaya, Malaysia organized by AMDI. It was aimed at informing the relevant ministries and institutions of the intention of USM to bring the technology of carbon ion therapy to Malaysia. The important conclusion from this dialogue was that all the participants agreed to the overall plan by USM. There was also a request that all participants who represented the leadership of various ministries were to inform their leaders about this dialogue and will let USM know the feedbacks later.

Proposed Financial Plans

The basic financial planning presented during the above dialogue will be mentioned here. AMDI has decided to choose carbon ion and has estimated the cost of carbon ion therapy infrastructure (ion source, LINAC,

synchrotron and treatment rooms) excluding the land and diagnostic facilities to be about RM450 millions (USD 140 millions). It is projected that, with less trials and errors during the construction, locally-paid Malaysian technical professionals, local building materials and locally-assembled non-critical parts will bring the cost lower than that of either a European or a Japanese facility. It was proposed that the three ministries, namely, the Ministry of Finance, the Ministry of Health and the Ministry of Science, Technology and Innovations to invest RM200 millions while private companies, private hospitals and joint-venture companies to provide the remaining RM 250 millions. The private conglomerate may be from outside Malaysia. The option is also open for Japanese investors to take the majority stake and manages the facility jointly with AMDI. In all cases, AMDI provides the land for the building, diagnostic facilities and the manpower, i.e. the local engineers, physicists, hospital support staffs and medical consultants. A number of international consultants need to be employed during the initial stage of the development and at the beginning of its operation. A comprehensive business plan will be developed later in collaboration with A2DX Co. Ltd. The development of carbon ion therapy facility is one of the top three priorities for AMDI.

Site Plans

There have been discussions on finding the most strategic location for the carbon ion facilities. A more viable site was thought to be within AMDI 112-acre campus itself. AMDI is in Bertam, a new township in the state of mainland Penang. The institute will serve as a medical referral centre for the northern region of Malaysia. The site planning and building will be quite similar to GHMC with the possibility of having a rotating treatment gantry. Thus, AMDI needs to consult the Japanese counterpart in the site planning. On reflection, Penang has always been a popular place for Japanese visitiors. The surrounding area of Bertam is well planned and a golf course is just next door to AMDI. A nearby highway provides an easy access to the north and south of Malaysian Peninsular. Penang airport is an international airport providing regular flights to Indonesian cities, Thailand and Singapore.

Evidently there are a number of heavy ion therapy centres around the world working closely with the medical faculty, technology faculty and teaching hospitals of various universities. This is because a carbon ion therapy centre is made up of three major components, i.e., the patient treatment (including diagnostic modalities), technology and research. A university is the most appropriate place to share these three components. Therefore AMDI fits well to the plan.

Challenges Ahead

In Malaysia, the level of acceptance of carbon ion as the treatment of choice varies. While a number of oncologists agree with the treatment modality, there are also ‘traditional’ oncologists who show less interest in carbon ion therapy as they are already used to the conventional x-ray/gamma/electron therapy. Such a feeling of anxiety is expected since they have not been trained in carbon ion therapy before. This is the first challenge. To some, proton therapy should be first introduced before carbon ion as proton therapy involves less energy in comparison to carbon ion. The energy of proton therapy is perhaps relatively easier to manage and references to many proton centres around the world are readily available. Carbon ion therapy possesses immense energy. It needs precision engineering, excellent physics, accurate positioning of spread-over Bragg peaks (SOBP) and rigorous training. Once a treatment is wrongly planned, a normal vital organ can be destroyed beyond repair. The carbon ion therapy committee of AMDI, however, respects such cautions in the interest of patient safety.

Nevertheless one needs to go forward, gathering all the ‘believers’ in carbon ion therapy along the way in order to proceed.

The second challenge is regarding the high technology required in the carbon ion therapy facilities - the synchrotron, beam production, raw materials, a demanding synchrotron maintenance and the technology transfer. The way forward is to collaborate with centres around the world, in particular, NIRS in Chiba. On the issue of technology transfer the AMDI believes in working together with NIRS – in the true spirit of Japanese tradition of honour and respect to each other. Malaysian oncologists, technologists, pharmacists and physicists need to be trained in places like NIRS.

Concluding Remarks

It is hoped that the next generation of Malaysian oncologists will have greater interests in heavy ion therapy. In order to progress forward , it is also hoped that Malaysia is a preferred country of Japan to transfer the heavy ion technology. It is a great honour for Malaysia if NIRS, other Japanese centres and international institutions prefer AMDI as their partner in promoting heavy ion therapy in the South-East-Asia.

Acknowledgements

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Future Plan of Heavy Ion Radiotherapy in Saudi Arabia

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Abstract

A heavy ion radiotherapy facility is planned at King Faisal Specialist Hospital and Research centre (KFSH&RC), Riyadh, Kingdom of Saudi Arabia. Various feasibility studies along with an IAEA expert mission were conducted for such a facility. All arrived at a favorable outcome recommending the realization of such a project, leading to its conceptual approval by the KFSH&RC Board of Directors. Acquisition and partnership details, funding issues, and final approval are being worked out.

Being the leading tertiary health care provider in the region, KFSH&RC constitutes the best site to host such a facility. The infrastructure of this project is already available at KFSH&RC and represented by greater than 25 years of experience in cyclotron technology, medical physics and radiation oncology. In addition, the recent approval for the 300-bed comprehensive King Abdullah Center for Oncology and Liver Disease project necessitates acquiring such a state of the art treatment facility to culminate uniqueness and hospital efforts towards patient care improvements.

This important facility would be a “transitional facility of excellence”, with enormous possibilities for advanced research, enabling “from the bench to the bed-side” activities. In addition, considering the geographical location of the Kingdom, practically between Europe and Japan, where the existing and planned facilities are situated, such a centre could provide advanced assistance to cancer patients not only in the region but also in other countries outside the region.

An introduction of the hosting institution and the status of the facility will be presented.

Expected Benefit and Efficiency of Treatment: CNAO Approach

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Abstract

Carbon ion radiotherapy is a safe and effective treatment. The role of carbon ion is well established in many rather rare tumours (mucosal melanoma, sacral and skull base chordoma, non squamocellular head and neck cancer, bone and soft tissue sarcoma of the trunk and of the head) and in some more common disease (initial stage non small cell lung cancer hepatocarcinoma, rectal cancer recurrence). Excellent results have been obtained in other cancers like prostate cancer, gynaecological malignancies but the role of carbon ion for these disease is still a matter of investigation. Other very aggressive cancers like pancreatic cancer and glioblastoma have been treated with carbon ion radiotherapy. In the past 5 years CNAO has been referring abroad patients with diseases that were not considered curable in Italy. Italian patients with advanced stage cancers in the head and neck, skull base, spine, liver and mediastinum that had no cure option have been successfully treated with carbon ions in Japan and Germany and with protons in France Switzerland and USA. During 2011 CNAO will start clinical activities and will initially focus on these patient for which carbon ion can be the best (and sometimes the only) option for cure.

Introduction

Carbon ion radiotherapy has been successfully employed in the past in Japan and in Germany (limited but interesting experience exist also in China). Excellent clinical results have been achieved in cancers that were not amenable to radical surgical resection but that did not show a high tendency to diffuse to the lymphnodes or to metastasize in different organs. In some occasion also tumors that have a high risk of distant metastasis could be treated successfully combining carbon ion radiotherapy with chemotherapy (mucosal malignant melanoma, osteosarcoma). A small proportion of cancer patients fulfill this criteria but as cancer is a very common disease the absolute number of these patient is still relevant. Many more patients have diseases in which there is a high risk of microscopic tumor infiltration. The role of carbon ion in these patients (locally advanced lung cancer, squamocellular carcinoma in the head and neck, etc.) is less well understood. Some other disease, like prostate cancer, can be treated with carbon ion with excellent result. It is difficult to assess if these results are better than those of other kind of radiotherapy without a direct comparison within a trial. Carbon ion radiotherapy can be significantly more expensive than other kinds of radiotherapy (mainly due to the high capital cost of the accelerating machines).

Indications in Italy

The Italian Radiation Oncology Society (AIRO) in 2003 has defined a list of eligible indications for carbon ion radiotherapy (Table 1). Subsequently indication shave been divided in two categories: (A) high priority and (B) potential indications. Category A consists of all the tumors in which the use of hadrontherapy is clearly demonstrated to be advantageous, being the only way to give a curative dose to the target volume minimizing the incidence of severe side effects. Category B consists of a great variety of tumors characterized mainly by a local evolution, with a limited probability of distant spread, and therefore potentially cured if the locoregional control can be obtained. Category A indication for carbon ion radiotherapy are listed in table 2.

Tumors	New pts / year	No. Eligible for carbon ions	% eligible for carbon ions
Salivary glands tumors	620	310	50%
Mucosal melanoma (head and neck)	30	30	100%
Bone sarcoma	520	52	10%
Soft tissue sarcoma	1’360	136	10%
NSCLC	31’000	1’550	5%
HCC	5’000	500	10%
Prostatic carcinoma	22’330	1’116	5%
Total	60’860	3’694	6%

Table 1: tentative indications for carbon ions radiotherapy

Tumors	New pts / year	No. Eligible for carbon ions	% eligible for carbon ions
Salivary glands tumors	620	310	50%
Mucosal melanoma (head and neck)	30	30	100%
Bone sarcoma	520	104	20%
Soft tissue sarcoma	1’360	272	20%
Maxillary sinuses adenocrcinoma	450	45	10%
Liver/Biliary tract/Pancreatic tumours	4’500	450	10%
Recurrent tumors	750	225	30%
Total	7’672	1’436	

Table 2: category A indications for carbon ions radiotherapy

Experimental phase

CNAO will be the first carbon ion facility in Italy. The Italian Ministry of health has requested that the efficacy and safety of CNAO as a tool to deliver carbon ion radiotherapy is proved in an experimental phase. This phase will last 18 months and will involve treatments of 230 patients (80 patients with protons and 150 with carbon ions). The goal of this experimental phase is to reproduce clinical experience of NIRS for carbon ion and of PSI for protons and therefore show the efficacy and safety of CNAO. During this experimental phase a cost analysis will be performed and it will be the basis to determine the Italian fee of carbon ion radiotherapy within the national health care system. The experimental phase will consist of prospective, non-randomized, single arm., single stage, phase II trials. Diseases treated with carbon ions will be: skull base chordoma and low-intermediate grade chondrosarcoma, spinal chordoma and low-intermediate grade chondrosarcoma, head and neck bone and soft tissue sarcoma, pelvis and trunk bone and soft tissue sarcoma, recurrent limb bone and soft tissue sarcoma ,salivary gland tumors, non mesenchymal tumors of the head and neck. Diseases treated with protons will be: skull base chordoma and low grade chondrosarcoma, spinal chordoma and low grade chondrosarcoma, meningioma. Primary endpoints of these trials will be tumor response and acute-intermediate toxicity. In the present experimental phase chemotherapy will not be employed and no pediatric cancer will be treated.

Routine operation

As soon as the experimental phase is completed concomitant chemotherapy and carbon ion radiotherapy will be used for malignant mucosal melanoma and pediatric solid cancer will be treated with protons. When a reimbursement fee has been established cost effectiveness analysis will be performed trying to account not only for the additional cost of carbon ion radiotherapy but also for the cost of recurrence treatment when a less effective therapy is

employed. In the medium long run there is the intention to investigate the role and efficacy of carbon ion in pancreatic cancer, gynecological cancer, prostate cancer, rectal cancer, mediastinal cancers, NSCLC (early stage) and glial tumors. There is also the plan to test the efficacy of carbon ion as anticipated boost in the treatment od head and neck locally advanced squamocellualr carcinoma and NSCL (locally advanced).

Conclusion

During the initial experimental phase and the subsequent routine operation CNAO will focus mainly on treating cancers in which carbon ion is the best (and sometimes the only) curative treatment. The role of carbon ion radiotherapy in more common disease will be investigated. As a reimbursement fee for carbon ion radiotherapy has not yet been decided the present Italian scenario does not permit meaningful quantitative cost effectiveness analysis.

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Cost Effectiveness of Carbon Ion Radiotherapy: Comparison with Other Treatments

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Abstract

The aim of this study was to evaluate the cost-effectiveness of carbon ion radiotherapy compared with conventional multimodality therapy in the treatment of patients with locally recurrent rectal cancer. Direct costs for diagnosis, recurrent treatment, follow-up, visits, supportive therapy, complications, and admission were computed for each individual using a sample of 25 patients presenting with local recurrent rectal cancer at the National Institute of Radiological Science (NIRS) and Gunma University Hospital (GUH). Patients received only radical surgery for primary rectal adenocarcinoma and had isolated unresectable pelvic recurrence. Fourteen and 11 patients receiving treatment for the local recurrence between 2003 and 2005 were followed retrospectively at NIRS and GUH, respectively. Treatment was carried out with carbon ion radiotherapy (CIRT) alone at NIRS, while multimodality therapy including three-dimensional conformal radiotherapy, chemotherapy and hyperthermia was performed at GUH. The 2-year overall survival rate was 85% and 55% for CIRT and multimodality treatment, respectively. The mean cost was ¥4,803,946 for the CIRT group and ¥4,611,100 for the multimodality treatment group. The incremental cost-effectiveness ratio for CIRT was ¥6,428 per 1% increase in survival. The median duration of total hospitalization was 37 days for CIRT and 66 days for the multimodality treatment group. In Conclusion**,** by calculating all direct costs, CIRT was found to be a potential cost effective treatment modality as compared to multimodality treatment for locally recurrent rectal cancer.

Introduction

Colorectal cancer is the fourth most common cancer worldwide and accounted for about 1 million new cases in 2002. In low-risk population, colon and rectal cancer rates are generally of the same magnitude.(1) In 2002, 34,889 and 41,000 cases of rectal cancer were registered in UK and USA, respectively.(2) In Japan, where rectal cancer comprises 14.6% of all lethal cancers, 31,990 cases were reported and predicted to increase to 51,206 by 2020, with a 2.91% annual growth of newly diagnosed cases.(3) After radical surgery for primary rectal cancer, the incidence of local recurrence is up to 33%. Although surgery is the mainstay of treatment for locally recurrent rectal cancer (LRRC), 70% of the patients die within 5 years following its diagnosis. Unfortunately, as a result of pelvic wall involvement, the local recurrence is often unresectable, which generally leads to a poorer outcome than resectable lesion. (4)

Due to the high recurrence rate and the high annual growth rate, the treatment strategy for LRRC is expected to become a major burden for health care systems. In developed countries, cancer-related costs and public

medical expenditures are increasing steadily owing to both increases in life expectancy and improved diagnostic and treatment options.(5)

For instance, preliminary data, from UK showed that spending on cancer treatment increased by 52% from 1990-91 to 2000-01, while total health spending increased 12%.(6) Total health costs were announced by the Japanese Ministry of Health, Labour and Welfare as amounting to roughly ¥21.87 trillion in 1995, rising to approximately ¥24.4 trillion in 2001 and 8.5% and 9.02%, respectively, were cancer-related.(7) Moreover, in USA, cost of colorectal cancer treatment alone represents 13.1% of total national expenditure on cancer treatment.(6)

Recently published data from the National Institute of Radiological Science (NIRS) in Chiba, Japan, showed that carbon ion radiotherapy (CIRT) for LRRC has 3-year and 5-year survival rates of 60% and 42.8%, respectively, and that it could be a promising alternative treatment modality next to surgery. (8) However, although the increased development of advanced technologies such as CIRT usually results in higher health care expenses, (9) cost-effectiveness of CIRT is rarely discussed. To date, only one cost-effectiveness study of CIRT has recently been published based on 10 patients with skull base chordoma. Although this only published study showed a cost- effectiveness ratio of carbon ion of €2,539 per 1% increase in survival, the study suffered from large uncertainty because direct costs were only estimated by standard reimbursement system. (10) In the present study, actual direct costs for diagnosis, treatment, follow-up, supportive therapy, complications and admission were retrospectively analyzed in 25 patients treated with CIRT at NIRS or multimodality therapy at Gunma University Hospital (GUH), Japan.

Materials and methods

Inclusion criteria

Between 2003 and 2005, medical records of all patients with unresectable recurrent tumors in the pelvis after radical surgery alone for primary rectal adenocarcinoma and no distant metastasis at the time of recurrence at NIRS and GUH, were studied. LRRC without distance metastasis was confirmed by computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) findings. Patients with recurrence in the colon were not included in the study due to the fact that the involvement of the colon could probably allow for reduced radiation doses to be applied. Furthermore, patients with another primary tumor, and infection at the tumor site and digestive tract adjacent to the clinical target volume were excluded. The location, stage and surgery of primary rectal cancer were considered in the inclusion criteria. These strict inclusion criteria, which allowed only 25 patients to be recruited in the study, were chosen to guarantee that the patients treated at GUH would have been equally suited for carbon ion therapy. The period between 2003 and 2005 was selected because in 2003 a lump-sum payment system based on Diagnosis Procedure Combinations (DPC) was introduced in 82 Japanese University Hospitals including GUH.

Diagnosis procedure combination (DPC)

DPC payment in brief contains two parts, prospective and fee-for-service payment. Prospective payment, approximately corresponding to the total payments for admission, is the sum of: hospitalization, 38.9%; injections, 11.0%; laboratory tests, 10.4%; diagnostic imaging, 6.6%; medication, 2.9%; procedures priced less than 1000 points (1 point = ¥ 10), 1.9%.

Fee-for-service payment, corresponding to the payment for the doctor’s fee and covering remaining 28.3% of the

fee, is the sum of surgery and its material costs, 18.2%, and additional services and treatments (procedures priced at 1000 points or higher, cardiac catheterization, endoscopy, radiotherapy, rehabilitation, etc.), 10.1%.(11) Fee-for-service payment depends on the national health insurance fee schedule. Prospective payment is paid per diem with a three-level step down based on the average length of stay for each diagnosis group. Furthermore, the prospective payment is adjusted by hospital coefficient, securing the previous year's payment in each hospital. (11, 12)

Conventional treatment at GUH

All patients were treated by multimodality treatment including three-dimensional conformal radiotherapy (3D-CRT), chemotherapy, and hyperthermia, which is a standard treatment for unresectable LRRC at GUH. External beam radiation therapy at a total dose of 50 Gy (n = 9) or 58 Gy (n = 2) was delivered to the whole pelvis. The radiation treatments consisted of 25-29 fractions of 2.0 Gy, delivered 5 days a week with a Lineac of 10MV. Chemotherapy consisted of 5-FU (250 mg/m2 per day) and LV (25 mg/m2 per day) administered by continuous infusion during the night for 5 days a week in the second and fourth weeks of radiation therapy. Hyperthermia (mean= 40.4ºC) once a week during the radiation therapy for an hour was performed by radiofrequency devices (Thermotron-RF 8, Yamamoto Vinita Co., Ltd., Osaka, Japan). (13) Consequently, all patients at GUH received chemo-thermo-radiation therapy as indicated by the standard treatment protocol. After being treated with chemo-thermo-radiation therapy, local resection for tumors was performed for three patients according to the treatment protocol at GUH. Therefore, only three patients received local resection for the recurrent tumors at GUH (2 abdminoperineal resection and 1 stapled lower anterior resection).

Carbon ion radiotherapy at NIRS

The patients were treated with carbon ion radiotherapy alone which is the standard treatment for LRRC at NIRS. A total radiation dose of 73.6 Gy (n = 13) or 70.4 (n = 1) in 16 fractions over 4 weeks was delivered to the tumors.

Treatment cost of recurrence

All patients in both treatment arms had undergone primary surgery alone, but calculation of the primary cost of the rectal cancer treatment is out of the scope of the present study. In order to assess the direct cost of recurrence; hospitalization (include Intensive Care Unit), radiation therapy, chemotherapy, hyperthermia, surgical treatment, medical laboratory and imagining investigations, visits, follow-up, medications, supportive therapy (physical, nutritional and medical) and consequential costs (medical reports, images copies and health education) were thoroughly calculated using the medical records.

However, indirect costs and costs of intangibles could not be evaluated in the current retrospective study. The indirect costs are lost resources, due illness effects on sick person and their support system such as lost production, days off work, sickness pay, invalidity or premature death. Intangible costs are the psychological aspects of disease as pain and suffering. (14) Therefore, since the present study is retrospective, only direct cost of two years of follow-up from the time of recurrence was calculated individually for each patient; afterwards an average cost of all patients in each group was analyzed. The mean cost for each treatment group CIRT (A) and for multimodality treatment (B) was calculated. Subsequently, incremental cost-effective ratio (ICER) which is expressed as the additional treatment costs of the new technique weighted by gain in outcome was analyzed.

$$ICER = Cost(A) - Cost(B) \Big/ effectiveness(A) - effectiveness(B)$$

The ICER can be based either on the gain in local control rates (ICER in terms of disease free survival) which can be used as a measure of disease free survival or on the overall survival rates (ICER per 1% increase in survival). Therefore, 5-year overall survival rate and 5-year local control rate from literature review were analyzed for both groups using the calculated mean costs for CIRT (A) and multimodality treatment (B). Re-recurrence cost was also estimated by multiplying the mean costs of CIRT (A) or multimodality treatment (B) by their re-recurrence probability in each group.

It is worth mentioning that the multimodality treatment cost at GUH refers to real total costs paid by both the National Health Insurance System of Japan and patient, while it refers to the real total costs paid by patient alone in case of carbon ion treatment since CIRT is still not under the coverage of the National Health Insurance System. (15)

Results

After initiation of local recurrence treatment, the 2-year overall survival rate was 85% for CIRT and 55% for multimodality treatment, as shown by Kaplan–Meier curve (Figure 1). According to the hazard ratio, the risk of dying in the multimodality treatment group was 1.4 of that in the carbon ion group. The 2-year local control rate was 100% in patients treated with CIRT at NIRS, while the local control rate could not be evaluated due to incomplete documentation of exact date of distant metastasis at GUH. However, all cost details related to the metastasis were well documented. The absolute values of the direct cost of recurrence for all patients in both groups are summarized in Table 1.

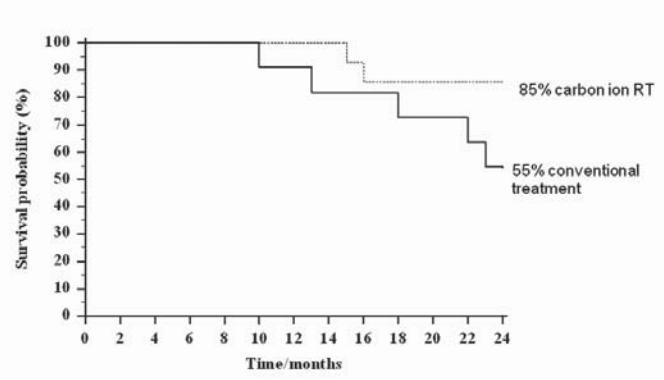

Figure1. Two-year overall survival curve for carbon ion radiotherapy group and conventional multimodality treatment group for locally recurrent rectal cancer.

Table 1. Days of admission an overall treatment cost for 25 patients

Carbon ion radiotherapy			Multimodality treatment		
Patient	Days of admission	Overall treatment cost/¥	Patient	Days of admission	Overall treatment cost/¥
1	37	3 975 810	1	186	8 218 177
2	44	4 371 820	2	123	8 137 957
3	79	4 730 760	3	76	2 768 777
4	36	4 397 980	4	80	3 337 060
5	36	5 388 630	5	61	4 443 295
6	37	4 121 600	6	44	7 058 167
7	47	4 326 490	7	66	3 780 787
8	116	7 646 510	8	75	5 284 419
9	33	3 976 610	9	38	1 801 837
10	32	4 059 100	10	51	1 843 487
11	36	4 945 020	11	64	4 048 137
12	70	5 786 900			
13	51	5 33 8210			
14	35	4 189 800			

Table 2. Breakdown of the direct costs

	Carbon ion RT		Multimodality treatment	
	Mean cost (¥)	Percentage (%)	Mean cost (¥)	Percentage (%)
Hospitalization cost (including DPC)	1 038 885	21.6	3 394 066	74.0
Food	66 154	01.4	114 795	02.5
Laboratory investigations	79 510	01.7	86 110	01.9
Imaging investigations	266 238	05.5	191 366	04.2
Radiotherapy	3 140 000	65.4	444 273	09.6
Chemotherapy	0	00.0	125 666	02.7
Hyperthermia	0	00.0	19 495	00.4
Surgery	0	00.0	24 384	00.5
Medication	57 435	01.2	186 584	04.0
Visit fee	14 028	00.3	13 063	00.3
Health education	48 297	01.0	11 298	00.2
Reports and image copies	93 399	01.9	0	0.00
Total (mean) (¥)	4 803 946		4 611 100	

DPC, diagnosis procedure combinations; RT, radiotherapy.

The ICER for CIRT based on the calculated survival rate was ¥6,428 per 1% increase in survival. The percentage of mean cost showed that 65% of the cost in the carbon ion group belonged to the direct CIRT cost, which was almost 7 times more than the photon radiation cost at GUH. On the other hand, the cost of prospective payment of DPC at GUH represented 74% of the total cost (Table 2). The median hospitalization duration was 66 days for the multimodality treatment group and 37 days for the CIRT group. Regarding the toxicities, no patients developed grade 2 or more acute and late toxicities for CIRT group. However, 4 and 2 patients developed grade 2 or more acute and late toxicities respectively in the multimodality treatment group.

Discussion

The current estimated cost of proton therapy has an average of €25,000 and cost ratio between proton treatment and intensity modulated photon irradiation is approximately 2.4. (15) Based on French ETOILE project, cost of carbon ion treatment per patient widely varied from €12,000 to 28,000 as a result of variation in fraction number and session duration. (16) However, our analysis showed that carbon ion radiotherapy alone, which is paid per treatment not per fraction, could be a cost-effective treatment modality for certain tumors that are typically treated by multimodality approach including three-dimensional conformal radiotherapy, such as LRRC. This cost effectiveness is related to costs of hospitalization and treatment related morbidity which generally was

found to be much lower in case of CIRT. (17) Our findings also showed significantly less days of admission (Table 1) and less toxicity for CIRT than multimodality treatment.

In fact, when treating LRRC, photon radiotherapy alone has not been shown to achieve significant survival benefit (18,19). For this reason the combination of conventional radiotherapy and chemotherapy is usually employed either for symptomatic or resectability improvement (20). Despite the use of multimodality therapy, 5-year survival rates of patients with LRRC remain 22-31% and local control rates 50-71% (21-24). On the other hand, CIRT alone has an overall survival rate of 42.8% and local control rate of 81% at 5 years (8). By analyzing these 5-year survival rates and local control rates based on our calculated mean cost of ¥4,803,946 for CIRT and ¥4,611,110 for multimodality treatment, CIRT seems a cost effective treatment modality for LRRC. In addition, the wide range of cost and high cost at GUH was mainly as a consequence of differences in survival (Figure 1) and variation in days of admission (Table 2) that could be linked to severity of treatment complications (Table 5). For example, the absolute costs for patients' number 1 and 2 in the multimodality treatment group were higher than other patients (about 8 million yen) due to their longer days of admission (table 1) compared to other patients including admission to Intensive Care Unit. The same applies to the patient number 8 in the carbon ion therapy group (table 1). On the other hand, patients' number 9 and 10 in the multimodality treatment group had a cost of about 1.8 million yen (table 1) because they had the least survival among the group and died within the first year (Figure 1).

The present study included all direct costs for two years of follow-up from the time of recurrence. Although, CIRT yielded better outcome, there was insignificant different between the mean cost of both treatment modalities. The calculated ICER in terms of gain in overall survival probability due to carbon ion RT is ¥6,428 per 1% increase in survival. Our analysis provides some evidence that carbon ion RT could be cost-effective in the treatment of LRRC. To the best of our knowledge, it is the first cost-effectiveness study of carbon ion beam RT including all direct costs. However, it is necessary to take account of the indirect costs as well, calling for future prospective studies. Yet, to perform prospective cost-effectiveness study before implementing a new technology is still an ethical concern (25-27).

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Medical Tourism in Heavy Ion Radiotherapy

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Development Bank of Japan estimates the market of medical tourism to be 550.7 billion yen (approximately $6.1 billion under currency rate of $1.00=90 yen) in 2020. Will this estimate come true? Will the wealthy around the world come to Japan for our health care? Is health care in Japan attractive enough to appeal to these people? Indeed, Japan ranked 1st among the 191 nations for its overall health system attainment as stated in the World Health Report 2000. This certainly is an honor granted by WHO that would catch attention of those who consider medical tourism as an option. However, what this encouraging statistics reflect is health care in Japan as a whole. Figures that tell details may bring somewhat different impression. For instance, when Japan and the United States were compared for cancer treatment, in-hospital death rate of diseases such as cerebral tumor and respiratory neoplasm differed by more than 30%. Calculation of this figure is conducted without risk adjustment, and some treatment methods were not included in the equation, one of which being heavy ion radiotherapy. If it were taken into account, would the result add even more glory to the honor? The race is on. Heavy ion radiotherapy in Japan faces the world, and its competence is judged in international level.

Development of Heavy-Ion Radiotherapy Technology in NIRS

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Heavy-ion beams have attracted growing interest as a suitable tool for deeply-seated cancer treatment not only due to their high dose localization at the Bragg peak, but also due to the high biological effect in this region. In 1946, Robert Wilson proposed the clinical application of the cyclotron, advocating the use of protons and heavier ions in treating human cancer. Lawrence Berkley National Laboratory (LBNL) had carried out the clinical study of cancer treatment with He-ion cancer in 1960s and with Ne ion in 1970s, which was the first heavy-ion cancer treatment in the world. Encouraged by the promising results from the pioneering work at LBLN, National Institute of Radiological Sciences (NIRS) proposed the construction of the HIMAC facility dedicated to the cancer radiotherapy. At that time, the cancer became the first cause of death in Japan in the early 1980s. Therefore, Japanese government approved the HIMAC project as one of projects of the "Comprehensive 10-Year Strategy for Cancer Control" that started in 1984. Completed in October 1993, HIMAC was the world's first heavy-ion accelerator facility dedicated to medical use. The carbon-ion radiotherapy with HIMAC was initiated in June 1994, after the beam commissioning and the pre-clinical study. As a result of the accumulated numbers of protocols, in 2003 the Japanese government approved carbon-ion radiotherapy with HIMAC as a highly advanced medical technology, which increased the expectation of the cancer patients as one of cancer treatment methods. NIRS therefore proposed a new facility to boost the application of carbon-ion radiotherapy, with the emphasis on a downsized system to reduce cost. The design and R&D works had been carried out from April 2004 to March 2006. On the basis of these works, Gunma University, in collaborating with NIRS, had constructed a pilot facility of the downsized carbon-ion radiotherapy facility since February 2007, and the clinical trial was successfully initiated in March 2010. NIRS, on the other hand, has been engaged in research on new treatments since April 2006 with a view to further development of the treatments at HIMAC. One of the most important aims of this project is to realize an "adaptive cancer radiotherapy" that can treat tumors accurately according to changing size and shape during a treatment period. NIRS, which treats both fixed and moving tumors, proposed a fast 3D rescanning method with gated irradiation as a move towards the goal of adaptive cancer radiotherapy for treating both kinds of tumor, and NIRS has developed the fast 3D scanning itself and rotating gantry with this scanning technology. Completing the development of these key-technologies, NIRS has constructed the new treatment research facility toward the clinical study with adaptive cancer therapy since 2007. In September 23rd, 2010, the first beam was obtained in the new treatment

research facility, and the beam commissioning and pre-clinical study have been carried out toward start of the clinical study in the next March.

Figure 1 shows the development flow of the heavy-ion cancer radiotherapy facility in Japan. Carbon-ion radiotherapy with HIMAC has treated more than 5, 500 pts since 1994. In these treatments, the new technologies such as the respiratory-gated irradiation and layer stacking irradiation methods, developed by NIRS, has applied to the cancer therapy with HIMAC. On the basis of the clinical study and the related technologies developed by NIRS, the downsized carbon-ion radiotherapy facility was developed and was constructed in Gunma University. One has expected the further developments of heavy-ion radiotherapy using a pilot facility in Gunma University and the new treatment research facility in NIRS, and these technologies will play an important role to heavy-ion cancer radiotherapy in the world.

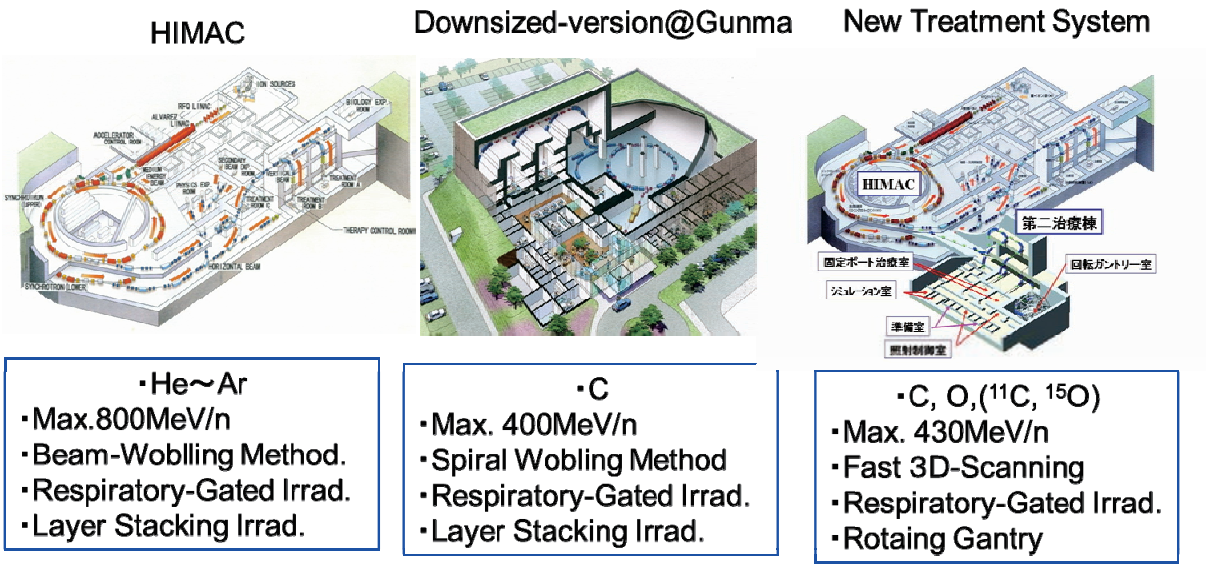

Fig. 1. Development flow on heavy-ion cancer radiotherapy technologies. The new technologies have been developed with the HIMAC facility dedicated to heavy-ion radiotherapy study, which brought the downsized facility constructed in Gunma University. The further development of heavy-ion radiotherapy with the new treatment research facility has strongly expected to play an important role of the cancer radiotherapy in the world.

Development of the Treatment Planning System for Spot Scanning Carbon Ion Therapy

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1. Introduction

The treatment planning system for radiotherapy assists in designing the shape of the target tumor in the patient's body and the irradiation procedures necessary for delivering the required dose. In order to make maximum advantage of the scanning irradiation method, new irradiation techniques should be developed for treatment planning system to be applicable for carbon ion radiotherapy. It is particular important that such new treatment planning system be capable of future continual modifications and updates, because there remain various ongoing research tasks to complete (our research center is the only facility conducting the scanning carbon ion therapy in Japan), and the ion beam therapy is still a subject of extensive research. Specifically, there remain scientific uncertainties as to the methods for estimating the ion beam dose distribution based on the biological effects of the ion beams. Accordingly, the new treatment planning system should be adjustable to the technical and scientific progress and development that will be made in these areas. The broad-beam carbon ion therapy performed since 1994 at the National Institute of Radiological Sciences (NIRS) has achieved excellent clinical results. Therefore, the new treatment planning system must be built on the technical continuity and compatible both with the current broad-beam irradiation procedures and with possible future modifications and adaptations mentioned earlier. This article provides an outline the treatment planning system that has been newly developed at NIRS, focusing on these aspects.

2. System Characteristics

We adopted the strategic policy to design and develop a *de-novo* treatment planning engine (incorporating dosimetry and dose optimization). It was also our strategic policy to create a user-friendly interface enabling easy prescription, evaluation, and operation for the radiation oncologists and other planners that would use the system on a daily basis. Therefore, we arrived at a conclusion to utilize a commercially available treatment planning system, and connect the dose calculation engine developed at NIRS to this system [1]. This allowed the operator to use the common interface for operating the treatment planning system to which the calculation algorithms for ion beam therapy were integrated. The treatment planning system reported here first reconstructs the three-dimensional contours of the target and normal tissue of concern. Then, the system's calculation engine optimizes the dose distribution based on the input values of the permissible dose limit assigned for each area. At the same time, the system determines the optimal scanning lines for the scanning irradiation, sending detailed instructions on the energy levels, fluence and locations of the spots to the beam irradiation system.

3. Beam Configurations

The carbon ion pencil beams used for spot scanning becomes spatially diverted due to multiple scattering effects and nuclear reactions, when they penetrate into the patient body. In the scanning irradiation, the dose for each spot within the radiation field results from the sum of multiple numbers of pencil beams. It follows that slight dose variations on the beam periphery may possibly affect the total dose when a large number of beams are applied. Therefore, we determined the three-dimensional dose distributions in water for the carbon ion beams used in therapy. We then reconstructed the distribution measurements as a combination of triple Gaussian models. We thus have successfully developed a highly precise method for calculating the dose distributions by applying the reconstructed dose distribution estimations for the beam source data [2].

4. Biological Effect Model

Cancer cells derived from the human salivary gland cell line were used for the biological effect model, taking note of the ongoing broad-beam model. The biological effects of ionizing radiation are principally determined by the absorbed dose. However, it is also known that the effects are influenced by microscopic variations in the spacial dose distribution. Linear energy transfer (LET), which designates the amount of energy deposited per unit length along the beam path, is often used as the indicator characterizing the spatial dose distribution. However, because LET provides no information on the lateral structure of the beam, the same LET values may result in different biological effects, depending on the type of particle. As explained in the previous section on beam configurations, the clinically applied pencil beams include various nuclides resulting from the nuclear reactions, which will complicate the process for evaluating the biological effects based on LET.

For these reasons, noting the usefulness of the microdosimetric kinetic model (MKM) as the indicator for microscopic and three-dimensional energy transfer, we explored the possibility for applying this model to the estimation of the dose distributions resulting from carbon ion beam. Consequently, we have successfully developed MKM2010, the high-precision model applicable for the treatment planning system for scanning therapy [4]. The use of MKM2010 has enabled highly precise modeling of the biological effects for the complex irradiation field of the scanning carbon ion therapy. The use of MKM2010 has also achieved a close relationship between the new biological effect model and those currently used for broad-beam irradiation. The energy transfer estimated by using MKM2010 can be measured by commercially-available tissue equivalent proportional counter. This means that the biological (clinical) effects estimated by MKM2010 for a given point within the irradiation field can be readily checked by physical measurement, and this offers a great advantage over other models.

5. Verification of the MKM2010 Performance

In early 2010, we carried out simulation experiments by using the test-model scanning ports temporarily installed in the HIMAC physics experiment room, and discovered a highly accurate agreement between the measured distribution of dose absorption in water equivalent phantom and the values estimated by MKM2010. In addition, we checked the distribution of depth survival rate for human salivary gland tumor cells, with the co-operation from the group of NIRS radiobiology researchers led by Dr. Y. Furusawa, and found an excellent compatibility between the measurements and estimations. We are going to reconfirm these effects at the new facility to be built before starting therapy. We are also engaged in converting the site-specific doses administered in the past cases of broad-beam therapy into the equivalent doses for the new treatment system as part of the preparation for starting the scanning carbon ion therapy.

6. Conclusion

The new treatment planning system developed for the scanning carbon ion therapy has successfully achieved a more precise estimation of physical and biological effects of the carbon ion pencil beam. The new system has also established an excellent continuity with the current broad-beam therapy. The new treatment planning system is in the late stage of preparation for the upcoming scanning irradiation.

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Next-generation Irradiation System at New Particle Therapy Research Facility in NIRS

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Since 1994, the carbon beam treatment has been continued at Heavy Ion Medical Accelerator in Chiba (HIMAC). The total number of patients treated is more than 5,000 in 2010. Based on more than ten years of experience with HIMAC, we have developed new treatment equipments toward adaptive cancer therapy with heavy ion at New Particle Therapy Research Facility in NIRS. There are three treatment rooms in the facility. Two of them are equipped with fixed beam delivery systems in both the horizontal and vertical directions, and the other will be equipped with a rotating gantry. The heavy ion beam is provided from the HIMAC upper synchrotron (Fig.1). Toward adaptive therapy, a 3D scanning method with a pencil beam is employed. The beam delivery system with has been improved for the 3D scanning, such as an extended flat top operation and a beam intensity modulation. A superconducting rotating gantry is also planned for the compactness.

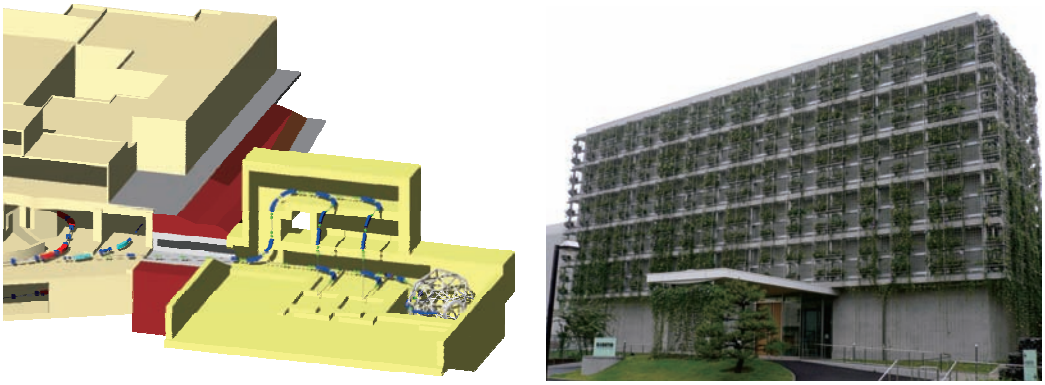

Fig. 1. Schematic view of the HIMAC and New Particle Therapy Research Facilities (left), and the photograph of the new building (right).

The maximum ion energy is designed to be 12^{C}, 430 MeV/n in both the horizontal and vertical beam-delivery systems, in order to obtain more than the residual range of 30 cm. The maximum lateral field and SOBP sizes are 22 cm x 22 cm and 15 cm, respectively, in order to cover the most of the treatments with HIMAC. The Fig.2 shows the horizontal and vertical irradiation ports for the treatment room E. The irradiation system is a 3D scanning method not only for a fixed target but also for a moving target. The phase-controlled rescanning (PCR) method is implemented and completes the several irradiation of one slice during a single gated period of the respiration.

The treatment tables with robotic arms are placed in the treatment room E and the CT simulation room for the precise positioning of the patients (Fig.3). The precision of the movement of the treatment table is less than 0.5 mm.

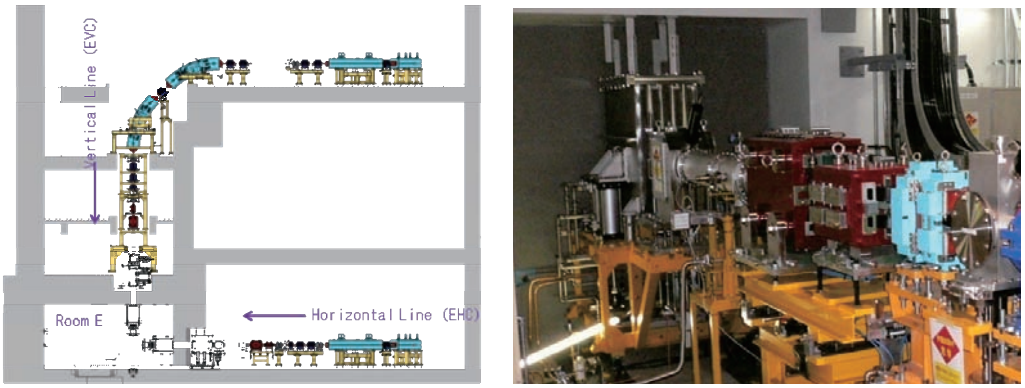

Fig.2. Schematic view of the horizontal and vertical irradiation ports for the treatment room E (left) and the view of the scanning magnet in the horizontal line (right).

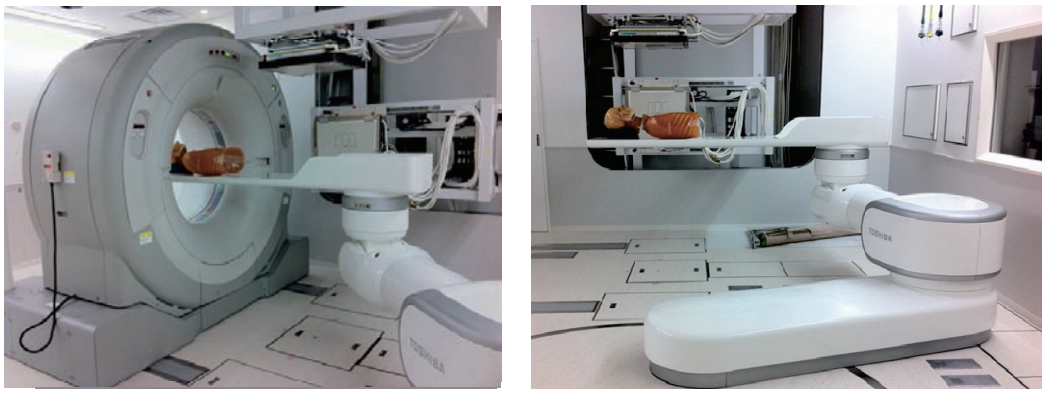

Fig. 3. Patient positioning system in the CT simulation room.

Recent Advances in Biological Experiments for Heavy-ion Radiotherapy

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The National Institute of Radiological Sciences (NIRS) has treated a substantial number of patients with cancer heavy-ion (carbon-ion) radiotherapy by HIMAC (Heavy Ion Medical Accelerator in Chiba) by now and is leading the world in this field both in terms of quality and quantity. As described elsewhere, the excellent treatment outcomes of the carbon-ion radiotherapy can be accounted for by the physical property of charged particles having a peak of energy deposition (Bragg peak) at the end of their track where carbon ions are specifically targeted around tumor site, while the surrounding normal tissues might be spared by minimal doses of radiation. This article will describe the biological mechanisms underlying the excellent effectiveness of the carbon-ion radiotherapy based on the recent research results on repair of DNA double-strand breaks (DSBs), cell cycle responses induced by heavy-ion irradiation.

Many studies have been published on repair of DNA DSBs induced by high linear energy transfer (LET) radiation (e.g., Rydberg et al. 1994, Taucher-Sholz et al. 1996). We have demonstrated that high-LET carbon-ion beams reduced the DSB repair efficiency in human cancer cell lines and other cells. Common methods for measuring DSB repair involve the use of gel electrophoresis, such as constant-field gel electrophoresis (CFGE). However, an increasing number of researchers are using gamma-H2AX foci assay recently which have been shown to be a highly sensitive indicator of DSBs (Rothkamm and Lobrich 2003). Figure 1 represents the formation and disappearance of DSBs induced by 1 Gy irradiation in human cells (Hamada et al. 2010). The results show that the disappearance of gamma-H2AX foci were much slower in cells exposed to high-LET carbon beams, suggesting that those cells had a poor DSB repair efficiency.

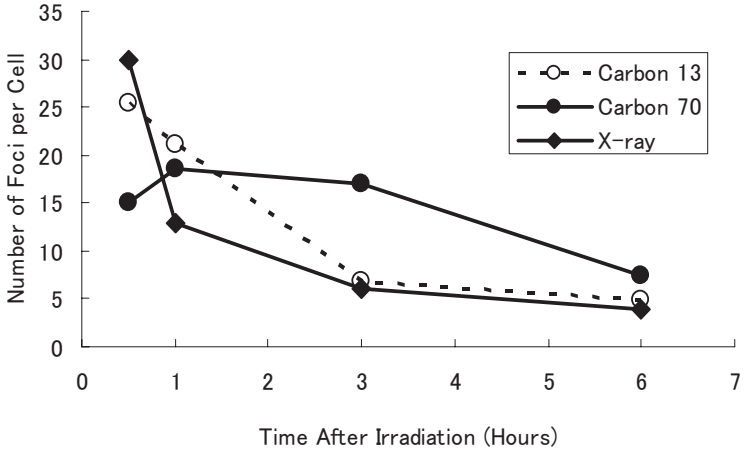

Figure 1. Time course of changes in the number of gamma-H2AX foci in human G1 cells irradiated with 1-Gy x-ray and carbon-ion beams (13 and 70 keV/μm).

On the other hand, the DSB repair efficiency of the cells exposed to low-LET beam (13 keV/μm) was higher than that of the cells exposed to high-LET beam, and similar to that of the cells exposed to x-rays. The low LET (13 keV/μm) portion (i.e., the plateau portion before the Bragg peak) may correspond to the area of normal cells in carbon-ion radiotherapy. Thus, less damage in normal cells might be observed than tumor cells where high LET radiation hits.

The inhibition of DSB repair is also manifested in chromosomal changes. We published studies that quantitatively evaluated the time course of changes in chromosome breaks following irradiation using premature chromosome condensation (PCC) technique (Okayasu et al. 2006, Sekine et al. 2008). Our study demonstrated that high LET heavy-ion beams induced high levels of remaining chromosome damage. Moreover, by combining the PCC technique and the fluorescence in situ hybridization (FISH) method (which is sometimes referred to as 'chromosome painting'), the frequency of chromosomal misrepair was quantitatively evaluated. The results showed that chromosome fragmentations definitively increased as a function of LET level, whereas the rates of chromosomal exchange were not significantly different between 13 and 70 keV/μm. These findings implicate the rate of chromosome misrejoining was not necessarily high in cells exposed to the high LET radiation commonly used in carbon-ion radiotherapy. Further studies in this area will be needed as it relates to the mechanism of post-irradiation development of secondary tumors.

It is well known that the radiosensitivity in mammalian cells exposed to low-LET radiation (e.g., x-ray, gamma-ray) is cell cycle dependent. Generally, cells are radioresistant in the late DNA synthetic (S) phase, and turn radiosensitive in the mitosis (M) phase. Some types of cells with an extended length of the Gap 1 (G1) phase may depict a second peak of radioresistance in the early G1 phase (Hall 2006). In a study using an accelerator at Berkeley, USA, Drs Bird and Burki found that variations in radiosensitivity throughout the cell cycle tended to diminish in cells exposed to high-LET radiation (Bird and Burki 1975).

Since experimentation on cell cycle is extremely laborious, until recently there were few studies reporting the heavy-ion effect on the cell cycle-dependent radiosensitivity after the Berkeley Lab experiment. A series of recent studies by Kato and collaborators shed a new light on this issue. We conducted an experiment to evaluate the change in the radiosensitivity of irradiated Chinese hamster ovary (CHO) cells using the NIRS's HIMAC; and the results are presented in Figure 2. CHO cells irradiated with 70 keV/μm carbon-ion beam showed significantly less variations in cell survival throughout the cell cycle in relation to X-rays. The curve became further flatter with increase in LET (Kato and Okayasu, unpublished data).

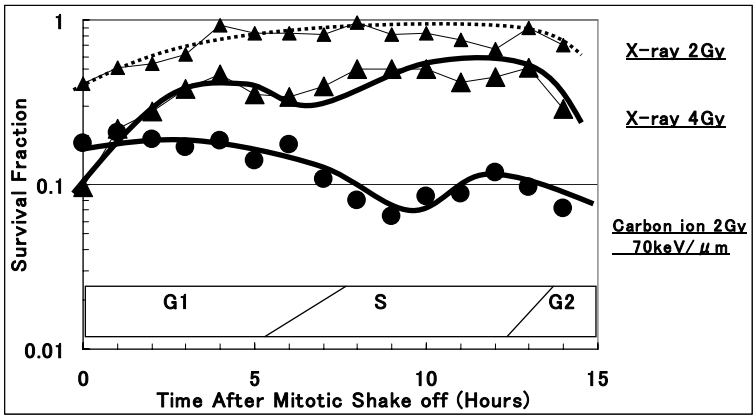

Figure 2. Time course of changes in radiosensitivity in Chinese hamster cells irradiated with x-ray and carbon-ion beam (70 kev/μm) emitted from the HIMAC accelerator (Kato et al. unpublished data). The data are plotted against the cell cycle.

Next, we conducted a similar study using CHO cells deficient in its typical DSB repair pathways: non-homologous end joining (NHEJ) and homologous recombination repair (HRR). The results indicated that the two major peaks of radioresistance were possibly related to NHEJ and HRR repair processes, and high-LET heavy ion radiation suppressed both the NHEJ and HRR repair processes. Overall, these results suggest that high-LET heavy ions cause complex DNA damage that may not be common in cells with low LET radiation, thereby exerting a difficulty in cell-intrinsic repair mechanisms, leading to severe biological consequences. Although it is evident that such heavy ion-induced damage causes high cell mortality, it remains to be determined whether the cell damage will lead to an increased risk of secondary tumors. Furthermore, very recent work from our laboratory revealed that high-LET heavy ions controlled tumor stem cells more efficiently than x-rays (Sai and Okayasu, personal communication). The heavy-ion effects on tumor stem cells seem to play an important role in tumor control in addition to repair suppression.

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Appendix

Outline of Existed Facilities

Institute / Hospital	Name of facility	Location (Country)	use	Start year	Total patients	Treat-ment rooms	Irradiatin port		
							H	V	Other
NIRS	HIMAC	Chiba (Japan)	Treatment, research	1994 -	5717 (Nov.2010)	3	2	2	0
GSI	SIS	Darmstadt (Germany)	Treatment, research	1997-2008	440	1	1	0	0
HIBMC	-	Hyogo (Japan)	Treatment, research	2001-	1820（P） 915（C） （Sep..'10)	5	2	1	3
IMP	HIRFL	Lanzhou (Chian)	Research, Treatment	2006-	126 (Nov. 2010)	2	1	1	0
University Hospital Heidelberg	HIT	Heidelberg (Germany)		2009-		3	2	0	1 Gantory
Gunma University	GHMC	Gunma (Japan)	Research and practice	2010-	90 (Dec. 2010)	3	2	3	0

NIRS National Institute of Radiological Sciences
HIMAC Heavy Ion Medical Accelerator in Chiba
GSI GSI Helmholtzzentrum für Schwerionenforschung GmbH
SIS SchwerIonen-Synchrotron
HIBMC Hyogo Ion Beam Medical Center
IMP Institute of Modern Physics
HIRFL Heavy Ion Research Facility in Lanzhou
HIT Hidelberg Ion Therapy Facility
GHMC Gunma University Heavy Ion Medical Center

Treated deseases	Irradiation method	Max. Energy MeV/u	Typical beam intensity from accelerator	Typical dose at patient	Typical patients / day	Operation schedule	Maintenance interval
whole body	Wobbler / Layer stacking	400	1.8E9 pps (typ. 0.3Hz)	2Gy/min. (5GyE/min.)	60 - 80	24 hours / 6 days / 10 month	2 / year
Brain, skull base	Scanning	400	variable	60	Variable	3 blocks/year	Variable
whole body	Wobbler	320（C） 230（He） 230（p）	3.33E8pps(C) 5.0E9pps(He) 2.0E10pps(p)	3GyE/min.	80-100	16hours/ 5days / 12 montth	4 / month
skin, bone and soft tissue, head and neck,liver, brain, sacrum chordoma, etc.	Wobbler / Layer stacking	100 for V 400 for H	1E8 pps X94, Y87	2.8-4Gy/min. (7-10GyE/min.)	around 20	24h/7day/ dependent	1 / year
	Rasterr scanning	430(C)					
whole body	Wobbler / Layer stacking	400	1.2E9 pps	3-5 GyE/fr	10 to 15	not decided	not decided

whole body; head&neck, skull base, bone&soft tissue, lung, liver, prostate, Rectum, Uterus, Eye, Brain

Outline of Facilities under Construction or Planning

Institute / Hospital	Name of facility	Location (Country)	Scheduled Start year	Scheduled 1st beam from accelerator	Expected patients per year	Ion species	Treatment rooms	Irradiatin port		
								H	V	Other
CNAO	CNAO	Pavia (Italy)	2011	first beam Oct. 2010	1500*	p, C	3	3	1	0
UKGM	PTC Marburg	Marburg (Germany)	2011			p, C	4	3		1 (45°)
UK S-H	NRoCK	Kiel (Germany)	2012				3	3	1	1 (45°)
Shanghai Particle Therapy Hospital		Shanghai (China)	2013	2012	1000	p, C	3	3	1	1
Kyushu International Heavy-Ion Treatment Center	SAGA HIMAT	Saga (Japan)	2013	2013	800	C	3	3	2	1 (45°)
EBG MedAustron Ltd.	MedAustron	Wiener Neustadt (Austria)	2015	2013	1200	p, C	3	2	1	p-gantry
Kanagawa Cancer Center	-	Kanagawa (Japan)	2015	2014	880	C	4	4	2	0
ETOILE	Centre ETOILE	Lyon (France)	Prevision: 2016		Prospective activity: 2000		3	2	0	2
KIRAMS		Busan (Korea)	2016 (Tentative)			C				
Mayo Clinic		Rochester, MN/ Phoenix, AZ (USA)	late 2014(p)	early 2014(p)	2480	p	8	2		8

CNAO Centro Nazionale Adroterapia Oncologica
UKGM University Hospital Giessen and Marburg ltd.
PTC Marburg Particle Therapy Centre Marburg
UK S-H University Medical-Center Schleswig-Holstein
NRoCK Nordeuropäisches Radioonkologisches Centrum Kiel
SAGA HIMAT SAGA Heavy Ion Medical Accelerator in Tosu
KIRAMS Korea Institute of Radiological and Medical Sciences

1500* experimental phase: 230 patients,
first year 600 patients ,
second year 1200 patients, regime 1500 patients

Target deseases	Irradiation method	Max. Energy MeV/u	Typical beam intensity from accelerator	Typical dose at patient	Typical patients / day	Operation schedule	Mainte-nance interval
whole body**	Active scanning	400	4E7-4E8pps (C) 1E8-1E9pps (p)	4 GyE	70 - 90	220 days per year	No stop is foreseen
whole body (planed)	raster scanning	430	3E8 pps (C) 2E10 pps (p)		180	16 / 6 days / 280 days (treatment) + Physics + Maintenance	2 / year
whole body	scanning	430	NA	NA	NA	16 hours /day 6 days / week 290 days / year	2 / year
whole body	beam scanning	430 (C) 250 (p)	1E9 pps (C) 2E10 pps (p)	not decided	60-80	12 hrs/day; 6 days/wk /11 mons/yr	1 / year
whole body	Wobbler / Layer stacking / Scanning*	400	1.3E9 pps (typ. 0.3Hz)	2Gy/min. (5GyE/min.)	60	12 hours / 5 days /240 days	
whole body	active scanning	400	4E8 pps (C) 1E10 pps (p)	2-5 Gy	<100	16 h/day 5 d/week	1 / year
whole body	Wobbler / Scanning	400	1.2E9 pps (typ. 0.3Hz)	2Gy/min. (5GyE/min.)	70 - 90*	15 hours / 5 days / 11 month	1 / year
whole body	Raster scanning if possible	400	ND	2Gy/min. (5GyE/min.)	80 - 100	14h/d , 5d/w for patients; 12 months	ND
whole body	pencil beam scanning	220	NA	1.5-2 Gy/min.	276	15hours/5 days /12 months	4 / year

whole body head&neck, skull base, bone&soft tissue, lung, liver, prostate, Rectum, Uterus, Eye, Brain
whole body** in the first phase no thoracic or abdominal lesion due to organ motion

Scanning* (Future extension)

70 - 90* Wobbler: 72 (24patient / 10h. x 3room) + Scanning: 14.5 (total 160 / year)