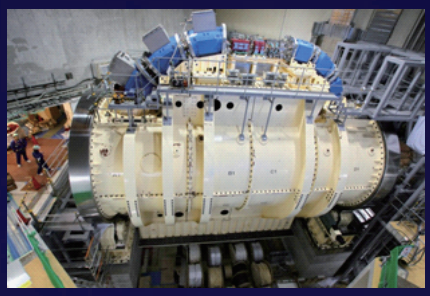
NIRS-M-283

2nd International Symposium on Heavy-Ion Radiotherapy and Advanced Technology

9 January 2016
Akiba Hall, Tokyo, Japan



Proceedings

NIRS

2nd Internatioinal Symposium on Heavy-Ion Radiotherapy and Advanced Technology

15th NIRS Heavy Ion Therapy Symposium

9 January 2016
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Proceedings

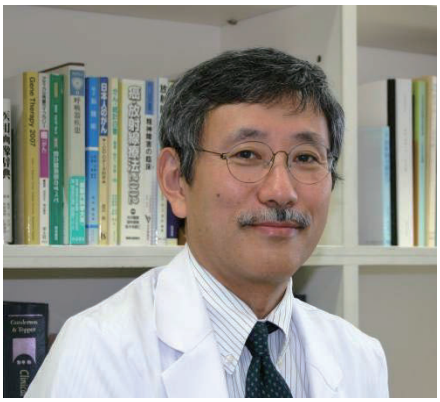
Organized by
Research Center for Charged Particle Therapy
National Institute of Radiological Sciences

Preface

I am pleased to welcome you all to the 2nd International Symposium on Heavy-Ion Radiotherapy and Technology. This symposium has been organized as an annual event of the Research Center for Charged Particle Therapy of the National Institute of Radiological Sciences (NIRS) in Japan. Since 1994, HIMAC has carried out clinical trials of cancer treatments using carbon ion beams. Having accumulated clinical experience in various types of malignant tumors, NIRS was successful in obtaining approval from the Ministry of Health, Labour and Welfare to carry out carbon ion radiotherapy as a "Highly Advanced Medical Technology" in 2003. Carbon ion radiotherapy has achieved for itself a solid place in the general practice of treating cancer. This year, the total number of patients will reach 10,000. In addition, NIRS started treatment with scanned carbon ion beams in 2011 and now we are installing the superconducting rotating gantry, working hard toward a more patient-friendly cancer therapy. For this event, we have invited experts in charge of carbon ion radiotherapy facilities both inside and outside Japan, which are either in operation, under construction, or in the planning stage, to introduce the current status and prospects of their facilities or plans. I believe this symposium will serve as a meaningful opportunity for all of us to share the latest information and future prospects, as well as exchange ideas for future development in this field.

Dr. Tadashi Kamada

Director of Research Center for Charged Particle Therapy, NIRS



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Sat. 9 January 2016 as of 2 December 2015

9:30 - 10:00	(30)	*Registration*			
10:00 - 10:10	(10)	**Opening Remarks**	Yoshiharu Yonekura	(NIRS)	
		Outline of Heavy Ion Radiotherapy	**Chair : Hirohiko Tsujii (NIRS)**		
10:10 - 10:30	(20)	Outline of Heavy Ion Radiotherapy	Tadashi Kamada	(NIRS)	
10:30 - 10:35	(5)	*Q&A*			
		Present Status at NIRS	**Chair : Hirohiko Tsujii (NIRS)**		
10:35 - 10:50	(15)	Present Status of Heavy-Ion Radiotherapy at NIRS - Clinical Experience -	Hiroshi Tsuji	(NIRS)	
10:50 - 11:05	(15)	Hardware Development and Medical Physics	Toshiyuki Shirai	(NIRS)	
11:05 - 11:20	(15)	Biological Models for Carbon-Ion Radiotherapy at NIRS	Naruhiro Matsufuji	(NIRS)	
11:20 - 11:35	(15)	*Q&A*			
11:35 - 12:45	(70)	*Lunch Break*			
		Clinical Experience at the Present Facilities	**Chair : Takashi Nakano (GHMC)**		
12:45 - 13:05	(20)	A Prospective Comparison between Proton and Carbon Ion Therapy for Hepatocellular Carcinoma	Tomoaki Okimoto	(HIBMC)	
13:05 - 13:25	(20)	Status Report of IMP	Guoqing Xiao	(IMP)	
13:25 - 13:45	(20)	Status Report of HIT	Semi Harrabi	(HIT)	
13:45 - 14:05	(20)	Recent Status of Heavy Ion Therapy at GHMC	Takashi Nakano	(GHMC)	
14:05 - 14:25	(20)	Status Report of the Italian National Center for Oncologic Hadrontherapy	Roberto Orecchia	(CNAO)	
14:25 - 14:45	(20)	Status Report of SAGA-HIMAT	Sho Kudo	(SAGA-HIMAT)	
14:45 - 15:05	(20)	Status Report of SPHIC	Jiade Lu	(SPHIC)	
15:05 - 15:35	(30)	*Break*			
		Future Prospects	**Chair : Kenji Nemoto (Yamagata Univ.)**		
15:35 - 15:50	(15)	Status Report of i-ROCK (Kanagawa)	Yuko Nakayama	(Kanagawa Cancer C.)	
15:50 - 16:05	(15)	Status Report of Carbon Ion Radiotherapy Facility at Yamagata University	Takeo Iwai	(Yamagata Univ.)	
16:05 - 16:20	(15)	Current Status of Carbon-Ion Radiotherapy Facility at Osaka	Kazuhiko Ogawa	(Osaka Univ.)	
16:20 - 16:35	(15)	Current Status of MedAustron	Ramona Mayer	(MedAustron)	
16:35 - 16:50	(15)	Current Status of KHIMA	Mi Sook Kim	(KIRAMS)	
16:50 - 17:05	(15)	Planning the Heavy Ion Therapy and Research Facility in Dallas, Texas	Hak Choy	(Univ. Texas SW)	
17:05 - 17:20	(15)	Future Prospects of UCSF	Reinhard Schulte	(Univ. California SF)	
17:20 - 17:30	(10)	**Closing Remarks**	Hirohiko Tsujii	(NIRS)	

CONTENTS

Outline of Heavy Ion Radiotherapy

Tadashi Kamada, MD, PhD

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Abstract

In 1994, CIRT (carbon ion radiotherapy) was begun at the NIRS (the National Institute of Radiological Sciences) using HIMAC (Heavy Ion Medical Accelerator in Chiba). As of March 2015, a total of 9,021 patients were treated with CIRT using HIMAC. The results have shown that CIRT has the ability to provide a sufficient dose to the tumor without unacceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to CIRT include locally advanced tumors and those with histologically non-squamous cell type of tumors. The efficacy of treatment regimen with small fractions in shorter treatment course has been also confirmed for almost all type of tumors in our experience. In so doing, we have found particular success in the treatment of difficult to cure, intractable cancers for which no other treatment options, and our results using this cutting-edge method of radiation therapy have attracted attention throughout the world.[1] New techniques those deserve attention as the next generation system are the spot scanning beam delivery and the compact superconducting magnet mounted rotating gantry. A clinical research using the spot scanning was already in operation with the original fully automated patient positioning system since May 2011. Good performance of the spot scanning beam delivery system has been confirmed. Regarding the compact superconducting magnet rotating gantry, the magnets were already made and have been testing at NIRS. The new gantry system will be expected to be in operation in early 2016.

Introduction

An idea of the use of ions for cancer therapy came from Cornelius Tobias, who was one of the first researchers to apply physical sciences background to the study of biology and medicine. Since the protons did not produce the biological effects much different from those of X-rays, it was then thought that heavier ion beams would have the dose localization advantage of proton beams and, in addition the potential benefit of high linear energy transfer beam. In 1975, the installation of the BEVALAC at LBNL, which provided therapeutic level heavy ion beams, an extensive series of radiobiological researches on several heavy ion beams were conducted, and in the same year, the first patient was treated with heavy ions by Joseph Castro. A total of 433 patients had received neon ion radiotherapy, he reported promising results with neon ion radiotherapy when compared with conventional radiotherapy for tumors arising from salivary gland, para-nasal sinus, bone and soft tissue, prostate, and biliary tract. However, the BEVALAC was shut down for lack of funds in 1992. The number of the patients treated with heavy ions was too small to give a definitive evidence for superiority of heavy ion beams in cancer therapy at that time.

On the other hand, in Japan, the decision was made in 1984 to build HIMAC at NIRS, which was the world's first heavy ion accelerator complex dedicated to medical use in a hospital environment. The accelerator complex took almost a decade to build and was completed by the end of 1993. A half year later, in June 1994, the first clinical trial using the carbon ion beams generated from the HIMAC was initiated for the locally advanced head and neck cancer.

Carbon Ion Radiotherapy at NIRS

Carbon ion radiotherapy at NIRS was initiated in June 1994. Until the present, almost 70 protocols have been conducted in an attempt to determine the optimal dose-fractionation and irradiation method for the treatment of the specific diseases. The number of patients has increased year by year, and the facility has meanwhile reached a capacity permitting 900 to 1000 patients to be treated in each year. The registration of patients totals 9,021 as of March 2015 and the categories of disease that can now be treated as a clinical practice include cancers of the skull base, the eye, the head and neck, the lung, the breast, the esophagus, the pancreas, the liver, uterine cancer, the prostate, the post operative pelvic recurrences of rectal cancer, and the bone and soft-tissue.

During the clinical trials with a small dose per fraction, at that time, average number of fraction was almost 18. All these early studies were carried out as a dose escalating study, and we found that we could give a very high dose per fraction safely in these early studies. And then the number of fraction has been tried to reduce. Average number of fraction was reduced from 18 to 11 to 12 for last several years. It is very effective to increase the number of treatment slot per year.

Future Prospect in Heavy Ion Therapy

Carbon ion therapy is a superior treatment modality for many cancers. Compared with other treatment modalities, however, it has to be admitted that carbon ion therapy is rather costly. The HIMAC with its 42 meter diameter synchrotron ring was built at costs amounting to roughly 33 billion yen. For the benefits of carbon ions to be available to the public at large, it is thus of paramount importance to develop a lower-cost and more compact system. In view of this, NIRS embarked on the development of a compact system that has the similar performance as the HIMAC but can be built at almost one third of the HIMAC in cost and size. In March 2010, we completed the new compact and low cost system at Gunma University in Japan realizing almost one third size and cost of the HIMAC, and is operating well with over 1800 cases treated. The next compact model was installed at the Ion Beam Therapy Center, SAGA HIMAT Foundation in 2013 and has successfully treated over 1,000 patients to date.

Further, as opposed to pursuing mere equipment miniaturization of the first generation HIMAC equipment, we are additionally developing the next generation of CIRT center, aiming to deliver respiration-synchronized rescanning beam therapy from a 360 degree freely-rotating gantry. In pursuit of this vision, we began a clinical trial of the scanning beam method on respiration-unaffected tumors in May 2011, finishing in November of the same year. During this trial, we noticed declining beam use efficiency and quality of the 20 cm range shifter in use, and so we developed a hybrid scanning system consisting of a 3 cm range shifter, with remaining changes in depth realized by beam energy modulation. To date over 700 cases have been treated with this hybrid system. In September 2015, we removed the range shifter entirely, and moved to delivering dose using full 200 different energy modulation.

With regard to the advanced scanning method, treating respiration-mobile disease remains a challenge. A markerless method of high speed rescanning irradiation has been developed: after analyzing the respiration cycle with a fluoroscope, and owing to improved equipment and methods used today at the HIMAC, respiration-synchronized tumor treatment has been realized at NIRS. Clinical trials began in March 2015.

With regard to the CIRT rotating gantry, though initial plans involved the installation of a normally-conducting magnet, we found the weight of the gantry could be limited to 300 tons through the use of superconducting magnets. At current the magnets have been produced, and gantry installation and assembly is underway, with completion planned for winter 2015. In terms of realizing new methods of radiotherapy, we expect that an even more powerful yet normal-tissue-friendly method of CIRT can be developed. By incorporating superconducting technology into the accelerator and overall device, we expect that within 10 years

we can produce a CIRT setup that fits within 20 square meters, which we call the "Super MINIMAC." This project is ongoing.

New Carbon Ion Radiotherapy Centers

Today, a new CIRT center is under development at the Kanagawa Prefectural Cancer Center, with plans to begin treatment by the end of 2015. Furthermore, Yamagata University, Osaka City, Okinawa Prefecture, and a variety of others are moving forward with plans to build their own CIRT facilities. Internationally, Austria plans to open a CIRT center in 2017, while South Korea, Taiwan and China among others are planning centers of their own. NIRS is actively collaborating with these centers and nations with regard to their construction and planning processes, and signing memorandums of collaboration (MOC) with a number of different institutes and universities of foreign countries. The United States National Institutes of Health (NIH) is also investigating the research potential of CIRT through the use of grants ("Planning for a National Center for Particle Beam Radiation Therapy Research2," P20), while the University of Texas Southwestern (UTSW) and University of California, San Francisco (UCSF) together are leading the North American Particle Therapy Alliance (NAPTA) in investigating the development of an CIRT facility for the U.S. NIRS is actively involved with both. At present, we are working on realizing an international clinical trial between the US and Japan: recruitment for a study of CIRT on advanced pancreatic cancer has just begun.

Conclusion

In the past 20 years, remarkable progress has been made in the development, both in knowledge and in delivery equipment, of heavy ion radiotherapy. Today, with CIRT recognized as an Advanced Medical Technology by the Japanese government and open for treatment of patients, we find that regardless of patients needing to pay out-of-pocket a relatively high cost for their cancer treatment, the number of patients arriving at our center continues to increase; that is, patients are increasingly seeking the benefits of a treatment modality that is easy on the body and offers high quality results. However, it is undeniable that a center capable of providing CIRT comes with high construction, operating, and maintenance costs. CIRT is currently under consideration for coverage by the Japanese National Health Insurance system, and for now our most important aim is for patients to have access to the most appropriate treatment for their condition, including CIRT. Accepting CIRT into the limited funding capacity of the national insurance system is by no means simple, and though debate is ongoing with and between officials, we are expecting success in the near future.

NIRS has studied the clinical benefits of heavy ion beams for more than 20 years, and today we are turning to the next generation of treatment and research. Though we have drastically reduced the costs of constructing a CIRT system, there are still high costs associated with maintenance and operation. A comparative study investigating the varying treatment modalities and protocols and their corresponding costs, as well as an evaluation of the utility of CIRT from a medical economics standpoint, is needed in the future.

Because the number of facilities that have implemented CIRT remains small and limited in experience, staff development and education at emerging centers domestic and abroad remains a significant concern. NIRS has a wealth of knowledge and experience built from the foundations of heavy ion beam research through to its clinical uses, and we are acting progressively as an IAEA collaboration center to assist in the dissemination of CIRT technology throughout the world.

References:

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Present Status of Heavy-Ion Radiotherapy at NIRS

- Clinical Experience -

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The National Institute of Radiological Sciences (NIRS) began clinical study on carbon-ion radiotherapy (CIRT) in 1994. More than 9,000 patients have been treated to date (Figure 1), and the benefits of CIRT over other treatment modalities have been demonstrated on various tumor sites in terms of low incidence of toxicity, high local control, and survival probabilities.

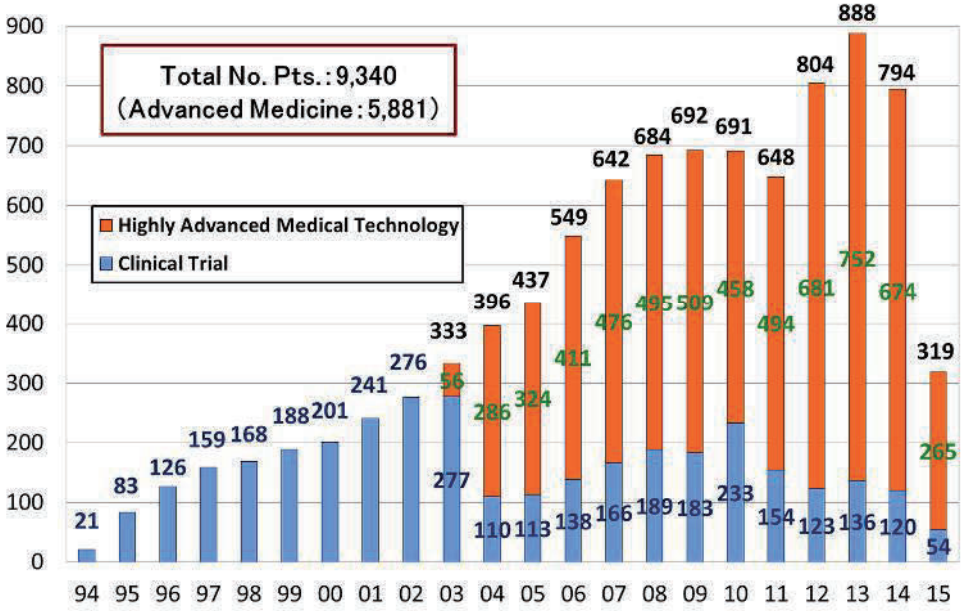

Figure 1. Number of patients treated with carbon ion radiotherapy at NIRS

Particularly, remarkable effectiveness on photon-resistant tumors, such as bone and soft tissue sarcomas, malignant melanoma, adenoidcystic carcinoma, and others, has been observed. In addition, substantially improved outcomes over x-ray therapy could be obtained by CIRT in terms of both anti-tumor effect and normal tissue toxicity for many other tumors, such as non-squamous cell head and neck cancers, pancreatic cancer, post-operative recurrence of rectal cancer, primary liver cancer, non-small cell lug cancer, and high-risk prostate cancer.

Furthermore, a significant reduction in overall treatment time and fraction number has been achieved with acceptable toxicities in many highly prevalent tumor sites, such as lung cancer, liver cancer, and prostate cancer.

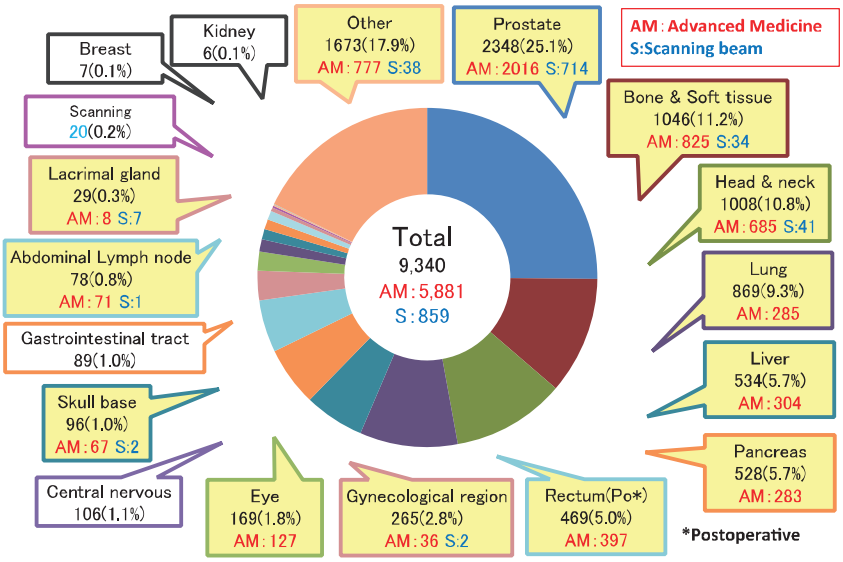

Figure 2. Number of patients treated with CIRT at NIRS by tumor sites

These achievements at NIRS have led to the promotion of CIRT in Japan. At present, three carbon therapy facilities other than the NIRS are in operation and another is under construction. Carbon treatment at the Hyogo Ion Beam Medical Center (HIBMC) was started in 2001, as the first facility to make available both proton and carbon therapy. A more compact facility was constructed at Gunma University Heavy Ion Medical Center (GHMC), with treatment starting in 2010. This was followed by construction of the SAGA Heavy Ion Medical Accelerator in Tosu (SAGA-HIMAT) in 2013. In these four facilities, the clinical efficacy of carbon ions is being prospectively investigated for a variety of tumors, with more than ten thousand patients having been treated by the end of 2013. The fifth facility for CIRT is being constructed in Kanagawa, named the Ion-beam Radiation Oncology Center in Kanagawa (iROCK), and treatment will start in March 2016. Furthermore, three other facilities are proposed for construction in Yamagata, Osaka, and Okinawa prefectures (Fig.3).

Thus far, the utility of CIRT in various tumor entities has been demonstrated by clinical studies at the Japanese institutes described above. Although each institute has distinctive facility features and treatment strategies, it is clear that CIRT can offer safer and/or more effective treatment to many cancer patients compared to x-ray therapy.

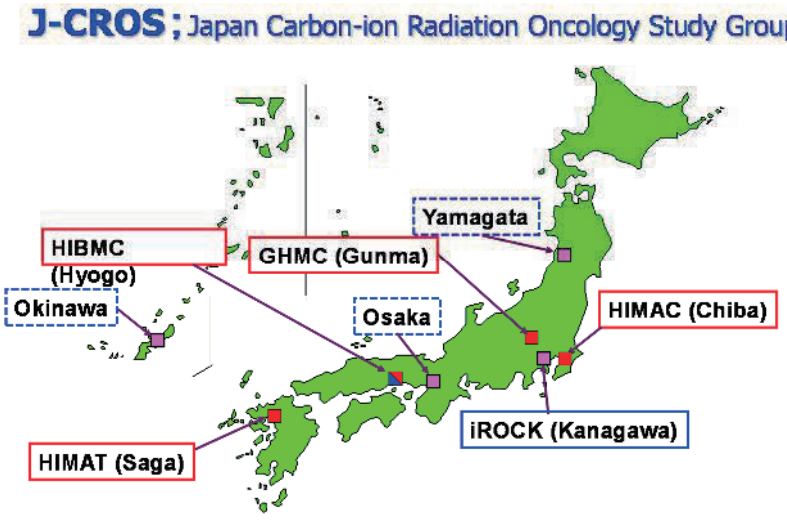

Figure 3. Location of running and planning CIRT facilities in Japan (Members of J-CROS)

Recently, multi-institutional clinical studies have begun to confirm the reliability and reproducibility of the NIRS' observed results. To this end, the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) was developed with the intent of conducting these multi-institutional cohort studies on tumors where existing evidence suggests improved outcomes with CIRT.

Table 1. J-CROS Activities

1. To establish a dedicated database system
2. To execute QA/QC program
3. To conduct clinical trials
   a) Retrospective data analysis in major tumor sites
   b) Prospective Phase II ~ Phase III studies in Pancreas, Liver, Lung, Rectum, Prostate
   c) Observational registry studies in B&S, H&N(non-SCC)
   d) Feasibility studies in Uterus, Kidney, Breast….

Initial steps included retrospective observational studies in various tumor sites, such as bone and soft tissue sarcoma, non-squamous head and neck tumor, lung cancer, liver cancer, rectal cancer, pancreas cancer, and prostate cancer. Data was gathered from all four active institutes, and then analyzed with regard to the efficacy and toxicity of CIRT (Table 2).

Table 2. Retrospective studies by J-CROS

J-CROS Protocols			
Study Design	**Protocol No.**	**Tumor Site**	**Materials**
Retrospective obsavational	J-CROS 1401 BS	Bone and Soft Tissue	Unresectable
	J-CROS 1402 HN	Head and Neck	Unresectable, except for sarcoma
	J-CROS 1403 NSCLC	Lung	Stage I non-small cell
	J-CROS 1404 NSCLC	Lung	Locally advanced non-small cell
	J-CROS 1405 HN	Head and Neck	Mucosal malignant melanoma
	J-CROS 1504 HCC	Liver	Unresectable, hepatocellular carcinoma
	J-CROS 1507 Rectum	Rectum	Post-operative locally recurrent
	J-CROS 1508 Prostate	Prostate	Localized, all risk

As a majority of the data originated from the NIRS, the results of these retrospective studies were similar to those independently conducted by NIRS; however, the reproducibility of the benefits of CIRT in various tumor sites could be confirmed.

Next, the J-CROS is planning a number of prospective studies for patients likely to benefit from CIRT according to the results of these retrospective studies (Table 3). We are optimistic that these activities will result in establishing multi-institutional standardization of carbon-ion radiotherapy.

It is required to register not only patients treated in these prospective studies, but also all other patients treated with CIRT at the facilities belonging to J-CROS. Therefore, J-CROS is preparing to establish a dedicated database in cooperation with JASTRO, the Japanese Society for Radiation Oncology. Furthermore, independently-reviewed quality assurance and quality control (QA/QC) of each facility's CIRT is important; the physics team of J-CROS has already prepared a QA/QC program that is now in operation.

Table 3. Planned prospective studies by J-CROS

J-CROS Protocols			
Study Design	**Protocol No.**	**Tumor Site**	**Notes**
Prospective	J-CROS 1501 NSCLC	Lung	Stage I, Peripheral non-snall cell
	J-CROS 1502 Pancreas	Pancreas	Locally advanced
	J-CROS 1503 Pancreas	Pancreas	Locally advanced
	J-CROS 1505 HCC	Liver	Unresectable
	J-CROS 1506 Rectum	Rectum	Post-operative locally recurrent
	J-CROS 1509 Prostate	Prostate	Localized high-risk
	J-CROS 1510 Prostate	Prostate	Localized low to intermadiate-risk
	J-CROS 1511 Gynecological region	Uterine Cervix	Cervical adenocarcinoma
	J-CROS 1512 Breast	Breast	Stage I, Low risk
	J-CROS 1513 HN	Head and Neck	Ear canal
	J-CROS 1514 Gynecological region	Uterine Cervix	Locall advanced scc
	J-CROS 1515 Gynecological region	Gynecoclogical Region	Mucosal malignant melanoma

In addition to these advancements in clinical study, a new treatment center equipped for scanning irradiation was completed at NIRS in 2010, with treatment beginning in 2011. For initial trials, scanning was applied only to tumors in the head-and-neck and pelvic regions, where respiration motion is minimal. However, developments at NIRS in high-speed scanning irradiation have enabled respiratory-synchronized scanning irradiation of mobile targets. A clinical trial to assess safety and efficacy was initiated earlier this year. Moreover, by incorporating superconducting magnets into the scanning irradiation delivery system design, we were able to design a relatively compact rotating gantry, which is currently being installed. In the near future, it will become possible to perform intensity-modulated ion therapy (IMIT) with the carbon-ion beam, that may currently be considered the "ultimate radiotherapy" with regard to dose concentration and distribution.

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Hardware Development and Medical Physics

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Abstract

The new facility (New Particle Therapy Research Facility) at the NIRS is equipped with an efficient carbon radiotherapy system including a compact rotating gantry, a fast 3D scanning irradiation system for moving targets, a precise treatment planning system for carbon scanning, a patient handling system with robotic arm treatment bed and a treatment management system. The treatment for the fixed target was started in May 2011 and the total number of the patients is more than 900. In 2015, the clinical trial for the moving target was started and the treatments of 10 patients are finished now. The depth scanning method is also changed in 2015 from the hybrid scanning to the energy scanning for the future improvement of the lateral dose distribution. The commissioning of the rotating gantry was started in October 2015. It adopts the superconducting magnets to reduce the size and weight. The superconducting magnets on the gantry are very stable and the commissioning is going well now.

Introduction

Since 1994, carbon beam treatment has been performed at the Heavy Ion Medical Accelerator in Chiba (HIMAC) [1]. Based on these experiences and research results, we have developed a new treatment system at the New Particle Therapy Research Facility at the National Institute of Radiological Sciences (NIRS). The new system irradiates the carbon beam by a 3D scanning system from any direction in order to improve the dose concentration in the target volume. Figure 1 shows the HIMAC facility and the new facility. The new facility has two treatment rooms (Rooms E. F) with fixed beam lines and one room (Rooms G) with a rotating gantry. All rooms are equipped with fast 3D scanning irradiation systems and robotic arm treatment beds. The maximum carbon energy is 430 MeV/n, in order to obtain a residual range of 30 cm.

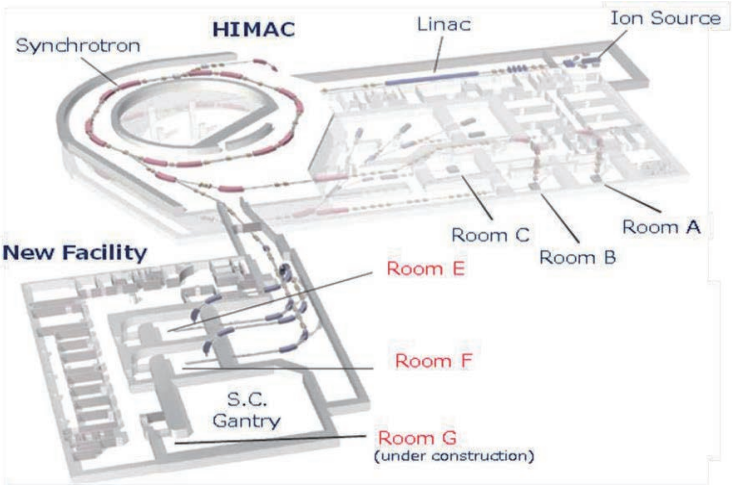

Fig. 1. A schematic view of the new facility (New Particle Therapy Research Facility) and the HIMAC facility. When completed, there will be three treatment rooms (E-G) in the new facility.

The project history is shown in Table 1. The project design was started in 2006 and the treatment at room E was started in May 2011. The number of the patients in the new facility is gradually increased and recently more than 50 irradiations per day are performed in two rooms. In 2015, the clinical trial for the moving target was started at Room F and the commissioning of the rotating gantry was stated. We also changed the depth scanning method from a hybrid scanning to energy scanning. I report the recent progress of the new facility.

Table 1: A brief history of the new facility

2006 /4	New facility project was started.	2013/4	Construction of gantry was started.
2009/2	Building construction was started.	2015/2	Clinical trial for moving target was started.
2010/9	First beam was delivered to Room E.	2015/9	Energy scanning was started.
2011/5	Treatment at Room E was started.	2015/10	First beam was delivered to Room G.
2012/9	Treatment at Room F was started.	2016/	Treatment at Room G will be started.

Energy Scanning

We had used a hybrid scanning method at Room E and F, where coarse tuning of the range was provided by an energy change of the synchrotron, while the fine tuning was provided by thin range shifter plates [2]. The dose conformity of the hybrid scanning is close to that of the energy scanning, where the range is changed by the beam energy directly from the synchrotron. Figure 2 shows the comparison of two methods. The hybrid scanning method has an advantage of the short commissioning period because the number of the beam energies is only 11. However, the scanning nozzle is large due to the range shifter box and it becomes an obstacle to improve the lateral dose distribution. We decided to adopt the energy scanning at Room G. Prior to that, we started the commissioning of the energy scanning at Room E, F in 2014 and changed the treatment operation in September 2015.

Figure 3 shows the commissioning results at Room E, F. The beam spot size is round and slightly smaller than that of the hybrid scanning but the DVH curves are almost same between two methods at Room E, F. The difference of the average RBE between two methods is less than 1 % and the energy scanning is slightly higher because the quantity of the fragment and the penumbra are smaller. The irradiation time is comparable because the beam energy is changed continuously (see Fig.2 right) and the time of the slice change is about 0.5 sec, which is comparable with that of the hybrid scanning.

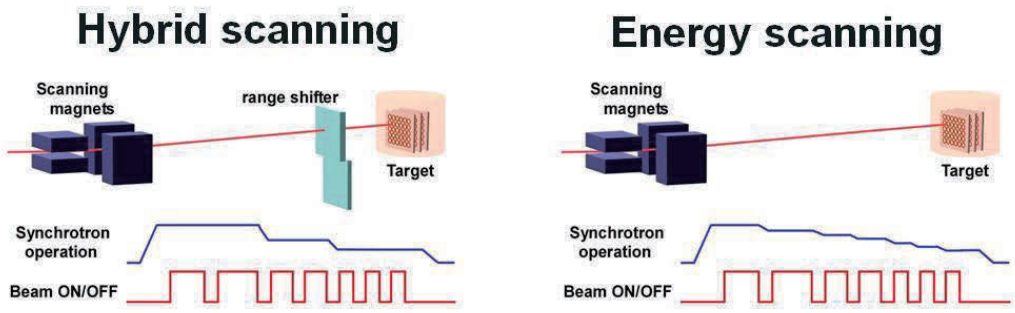

Fig. 2. A schematic diagram of the two depth scanning methods, the hybrid scanning and the energy scanning. The hybrid scanning uses 11 energies (140-430 MeV/n) and the range shifter (<50mm). The energy scanning uses 200 energies (62-430 MeV/n).

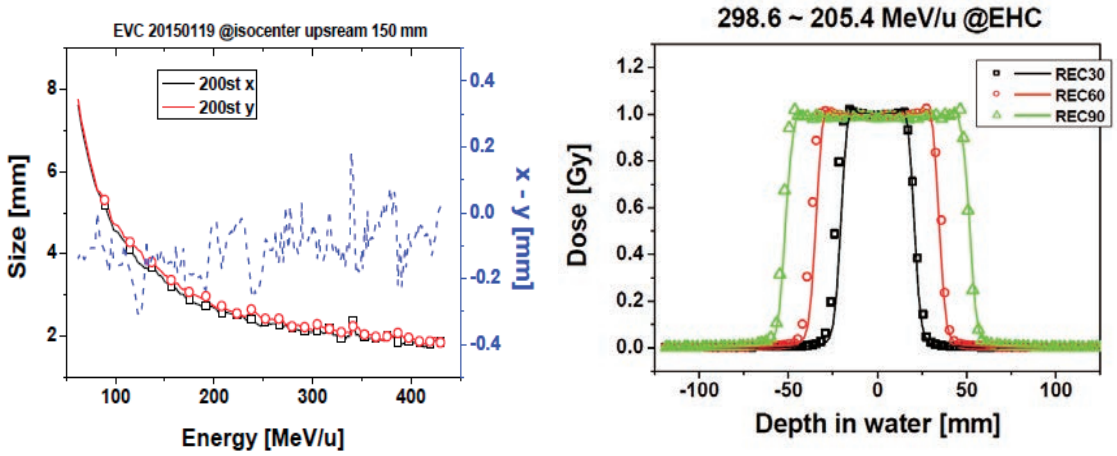

Fig. 3. The commissioning results of the energy scanning. The spot size was measured at 150 mm upstream from the isocenter (left) and the lateral dose distribution (right) were measured with various target size at Room E, F. The symbols are measured values and the solid lines are calculated dose by TPS.

Moving Target Irradiation

For the moving target irradiation, we adopted the rescanning method with a gating. The time for the rescanning irradiation of each slice is matched to the gating duration, which is called phase-controlled rescanning (PCR) [3]. The 3D scanning system is enough fast to fulfill this condition. We added a definition for the beam field-specific target volume (FTV) in TPS based on 4D-CT images [4]. The tumor tracking system using fluoroscopic images is adopted as a precise gating device in the treatment room [5]. It utilizes a multiple template matching method and can work without metallic markers.

After the commissioning of the treatment system, the clinical trial was started in February 2015. In the patient specific QA, all the planed beams are measured by a 2D ionization chamber array at several depths and compared with the plan dose. We add the extra patient specific QA for this clinical trial using the 2D ionization chamber array with acrylic wedges (see Fig.4 left). The 2D array is moved by the stage according to the patient respiration waveform. We can measure the lateral and depth dose distribution for the moving target at the same time and the results are compared with the plan dose.

Until November 2015, the number of the patient in the clinical trial is 10 at total. The details are 4 from lung cancer, 4 from liver cancer and 2 from cancers of bones and soft tissues. The clinical trial for pancreas cancer is also scheduled.

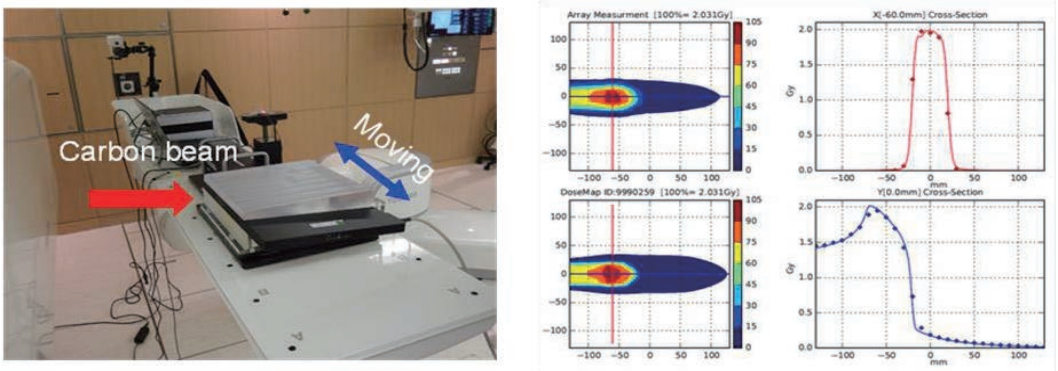

Fig. 4. Setup of the extra patient specific QA for the moving target irradiation (left) and the comparison between the measurements (symbols) and the recalculated dose (solid lines) by TPS (right).

Rotating Gantry

A rotating gantry is an attractive tool for radiotherapy, because targets are irradiated from desirable directions. However, it is difficult to realize it for carbon radiotherapy due to the high magnetic rigidity of carbon beams. The design of a compact isocentric rotating gantry was started at 2011 and combined function superconducting magnets have been developed [6]. The construction of the gantry was started in April 2013 in Toshiba and the transportation and the installation of the rotating gantry was started in January 2015 at the new facility. After the assembling, the superconducting magnets on the gantry were cooled down to 4K in July 2015. The first beam was delivered to Room G in October 2015 and the commissioning is going on.

The rotating gantry and Room G are shown in Fig.5. The length and radius of the gantry is 13 and 5.5 m, respectively. The 10 superconducting magnets on the gantry transport the carbon beam to the isocenter in Room G. The fast 3D scanning irradiation system, the markerless X-ray respiratory gating system and the robotic arm treatment bed are available in Room G as well as Room E, F. The maximum beam energy is 430 MeV/n and the maximum field size is 180 x 180 mm^2.

There are three important design items in this rotating gantry.

1. Stable operation of the superconducting magnets under the rotational motion and the field ramping.
2. Improvement of the lateral dose distribution.
3. Shortening of the commissioning period.

During the commissioning, the superconducting magnets are very stable and we never meet a quench in the rotation of the gantry. The field ramping speed is enough fast for the clinical use. When the field was changed from 430 to 56 MeV/u in 60 sec, the average temperature of the coil kept about 4K and the quench does not occurred. The reduction of the spot size is necessary to improve the lateral dose distribution. We remove the range shifter and replace the beam monitors to thin ones in the scanning nozzle. We also shorten the distance between a patient and snout. The measured beam size at the isocenter in Room G is about 3 mm (1σ) with 56 MeV/n, which is less than half of that of Room E, F. The number of the commissioning conditions for the gantry is very large with 200 beam energies and 360 degree rotation. We are testing the emittance equalization technique between horizontal and vertical ones [7]. We can use the same optics parameters at any gantry angles and greatly reduce the parameters by this method.

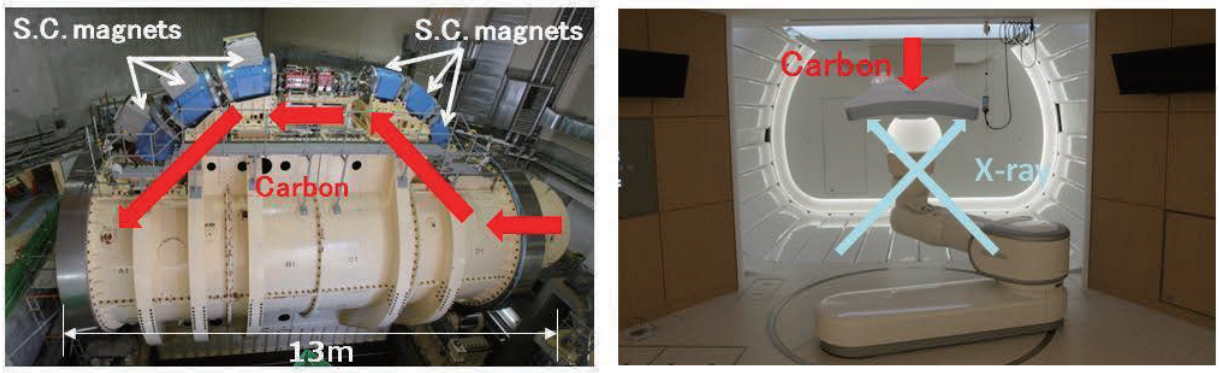

Fig. 5. Rotating gantry with superconducting magnets (left) and Room G (right).

Conclusion

In 2015, the clinical trial for the moving target and the commissioning of the rotating gantry were started. The project of the new facility is close to finish but some issues still remain such as the establishment of the regular operation for the gated scanning irradiation and Room G with rotating gantry. The optimization of the treatment planning to utilize the feature of the rotating gantry is also an important issue for carbon therapy.

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Biological Models for Carbon-Ion Radiotherapy at NIRS

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Abstract

In conducting carbon-ion radiotherapy (C-ion RT), it is indispensable to handle the change in the biological effectiveness appropriately. At National Institute of Radiological Sciences (NIRS), a pragmatic biological model, based on Human Salivary Gland (HSG) cell response coupled with clinical experience from fast neutron radiotherapy, was developed and utilized. The clinical outcome was in good agreement with the model expectation. The model has been upgraded to optimize its application to the technique of scanning irradiation. The new model offers versatile estimation of the biological effectiveness of various radiations based on their microdosimetric information, while harmonizing with the original approach. The overview on these activities will be presented.

Introduction

It is a requisite in treatment planning system (TPS) for the successful C-ion RT to understand and control the changing relative biological effectiveness (RBE) of the beam in the irradiation field. Under limited information available for the RBE of the carbon-ion beam, at NIRS a pragmatic RBE model[1] was established in initiating C-ion RT with broad-beam irradiation technique in 1994. In this original model the dose distribution of therapeutic carbon-ion beams was designed based on representative *in-vitro* HSG cell survival response. The HSG response was scaled to clinical response by making use of biological and clinical response for another high-LET radiation, fast neutron. Based on accumulated clinical outcomes as well as physical and biological knowledge related to the C-ion RT, the applicability of the model was evaluated, then further updated by taking into account the microdosimetric concept.

Materials and Methods

The designed RBE distribution with the original model was simply dependent on the irradiation depth and thus useful in reducing the number of parameters in the analysis of the clinical results. The RBE value expected by the model was then com-pared with the clinical outcomes in terms of tumor control probability (TCP). The biological model was updated when new scanning irradiation method was introduced in 2011. The new model was aimed at improving oversimplified approximation introduced in the original model in order to make maximum advantage of the flexibility of the scanning irradiation method. At the same time it was strongly necessary for the new model to harmonize with the original model in order to make maximum advantage of the vast clinical outcomes achieved under the original model. Under these requirements, we developed the new RBE model for C-ion RT, MKM2010[2] which is the update of the Microdosimetric Kinetic Model (MKM)[3] to be applicable systematically for any radiation.

Results

By analyzing the local control rate of non-small cell lung cancer observed in dose-escalation study with a TCP model, clinical RBE of C-ion RT was evaluated. The value was in good agreement with the model expectation[4] which supports the appropriate RBE estimation with the original model.

Parameters required in MKM2010 are intrinsic radiosensitivity α_0 and β and cell nucleus radius r_{cell} for biology, and absorbed dose D, lineal energy y and domain size r_d for microdosimetry. By choosing the appropriate domain size r_d, MKM2010 realizes versatile estimation of the RBE at any point and time even in highly complex irradiation field (Figure 1). The parameters in MKM2010 can be assessed experimentally and/or theoretically, it is useful in understanding the mechanism of RBE for various therapeutic radiations. In order to retain the continuity, the absorbed dose estimated with MKM2010 was scaled to that by original model at the center of the target[5]. Now MKM2010 has been implemented in TPSs for both broad-beam and scanning irradiation for C-ion RT at NIRS. Figure 2 shows an image of a 150 mm SOBP ridge filter for broad-beam port designed with MKM2010.

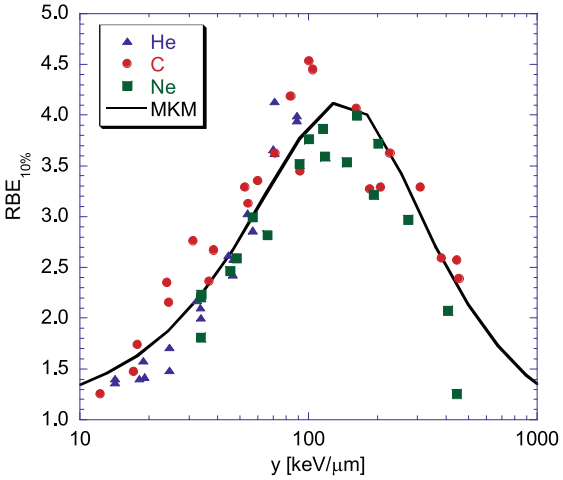

Figure 1. RBE of HSG for various ions with MKM2010 estimation

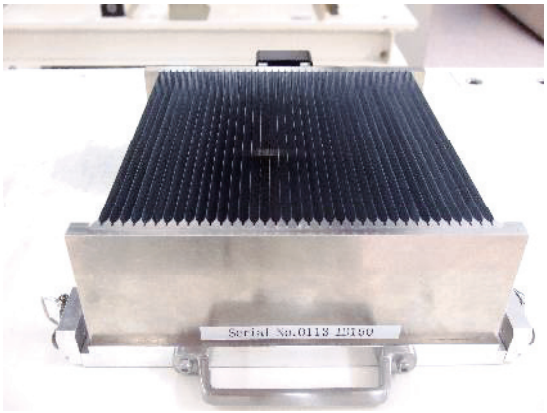

Figure 2. Manufactured ridge filter for broad-beam irradiation port (150mm SOBP)

Conclusion

The original RBE model developed for C-ion RT at NIRS worked successfully for therapeutic purpose. The updated model MKM2010, based on the microdosimetric concept, has achieved more accurate estimation with mechanistic approach while harmonizing the dose prescription with the original model.

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A Prospective Comparison between Proton and Carbon Ion Therapy for Hepatocellular Carcinoma

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Abstract

The Hyogo Ion Beam Medical Center (HIBMC) is the first institution in the world that can use both PT and CIT. Our important mission is to compare the proton therapy (PT) and the carbon ion therapy (CIT). The purpose of this study was to prospectively compare the efficacy and toxicity of PT and CIT in patients with HCC at a single institution. Both PT and CIT employed a protocol of 66 GyE in 10 fractions. The primary endpoint was local control (LC). The secondary endpoints included overall survival (OS) and safety. The interim analysis showed that both PT and CIT for HCC were effective and safe. There were no significant differences between PT and CIT in terms of efficacy or toxicity.

Introduction

Both proton therapy (PT) and carbon ion therapy (CIT) have demonstrated excellent clinical outcomes for the treatment of hepatocellular carcinoma (HCC). The purpose of this study was to prospectively compare the efficacy and toxicity of PT and CIT in patients with HCC at a single institution.

Materials and Methods

Patients with previously untreated HCC not adjacent to the porta hepatis or gastrointestinal tract were assigned to receive PT or CIT using propensity score matching by age, gender, liver damage grade, and tumor size. Both PT and CIT employed a protocol of 66 GyE in 10 fractions. The primary endpoint was local control (LC). The secondary endpoints included overall survival (OS) and safety.

Results

Thus far, 52 patients have been enrolled in the study. Twenty-four patients were assigned to receive PT; however, one was excluded from the study because of a switch to another protocol as determined by clinical judgment. Twenty-eight patients were assigned to receive CIT; however, two were excluded from the study because of participant refusal after his consent and discontinuation of the protocol due to a femoral fracture. Therefore, 23 PT

and 26 CIT patients were included in this interim analysis. The median follow-up time was 12.5 months in the PT arm and 14.2 months in the CIT arm (P = 0.445). The 1 and 2 year LC rates, respectively, were 100% and 100% in the PT arm and 100% and 100% in the CIT arm (P < 0.001). The 1 and 2 year OS rates, respectively, were 93.3% and 79.0% in the PT arm and 100% and 81.5% in the CIT arm (P = 0.499). For adverse events, radiation dermatitis was observed only at grade 2 or less. No patients experienced treatment interruption due to acute reactions, and all patients completed the planned radiotherapy. The rates of late dermatitis in the PT and CIT arms (43.4% vs. 42.3%, respectively) were similar.

Conclusions

The interim analysis showed that both PT and CIT for HCC were effective and safe. There were no significant differences between PT and CIT in terms of efficacy or toxicity.

Status Report of IMP

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Status Report of HIT

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Abstract

With this report we would like to provide insights into the current technical and medical status of the Heidelberg Ion-Beam Therapy Center (HIT). HIT officially opened on November 2, 2009, treating the first patients with a horizontal beam line. In October 2012 HIT started operating the worldwide first 360° rotating beam delivery system for heavy ions (gantry). Up to now, a little more than six years later, more than 3,250 patients have been treated with either carbon ion or proton radiotherapy. The main indications included adenoid cystic carcinoma, tumours of the central nervous system, chordoma and chondrosarcoma of the skull base or pelvis, prostate cancer and paediatric entities. All patients were treated using the intensity-controlled rasterscanning technique by dividing the target volume in virtual isoenergetic slices which are subdivided into a raster of voxel points. For scanning maximum beam energies of 221 MeV/u for protons and 430 MeV/u for carbon ions are available. The typical treatment schedule provides 12 hours of clinical operation, 6 days per week, enabling treatment of up to 70 patients per day. The HIT facility is fully integrated in the clinical and scientific environment of the Heidelberg Campus inter alia the University Hospital, the National Center of Tumour Diseases (NCT) and the German Cancer Research Center (DKFZ). Most of the patients are treated within clinical trials addressing the still many unanswered questions to further define and consolidate the role of particle therapy in radiation oncology.

Recent Status of Heavy Ion Therapy at GHMC

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Abstract

The Gunma University started heavy ion therapy with so-called concise heavy ion therapy facility from March 2010 and A total of 1486 patients were treated with carbon beam therapy at GHMC from March 2010 up to end of 2014. According to the site of the tumor, there were 878 prostate cancers, 121 lung cancers, 104 liver cancers, 118 head and neck cancers, 90 bone and soft tissue sarcomas, and 175 other cancers. 2-year biochemical relapse free survival rate of 304 patients with prostate cancers was 97.0% and biochemical failures occurred in 9 patients and no local failure and 4 distant metastases were observed. There was no patient experienced with grade 3 or more toxicity in Gastrointestinal and genitourinary organs. Grade 2 toxicity were seen in only 1 patient (0.3%) for Gastrointestinal organs and 14 (4.6 %) for genitourinary organs.

The 2year local control rate of 55 patients with liver cancers (Child Phgh score: A:47 (85%), B:8 (15%)) was 81.8% and the 2y over-all survival rate was 78.2%. There was no acute and late reaction greater than G2.

The 2 year local control rate of 53 patients with lung cancers (T1:36 patients, T2: 17 patients), was 89% and aver all survival rate was 85%. Grade 2 to 3 pneumonitis (CTCAEv4) were observed in about 4% of the patients. A high–precision heavy ion micro-surgery system has been developing in the room and a 1σ = 1.4 mm wide beam spot and beam depth control with 0.1mm precision was achieved.

Introduction

In radiation therapy, advanced radiation therapy technique for increasing the concentration of the dose to the cancer lesion was remarkable progress and "radiation therapy to cure cancer with preserving organ", so-called is in the spotlight. In these advanced radiation therapy, heavy ion radiotherapy has been recognized as the radiotherapy with superior dose convergence and the high biological effectiveness and is one of the minimally invasive treatments that gives best QOL after treatment in addition to a strong biological ability to control cancer. Japan is leading internationally this innovative treatment modality and heavy ion therapy will become an important radiation therapy for cancer in the near future.

Heavy ion therapy is a treatment that accelerates ions with a molecular weight larger than helium, such as carbon ions, to nearly 70 percent of the speed of light to penetrate human body and to reach deep seated tumors is used to treat cancer. Heavy ions have two major characteristic advantages that differentiate them from X-rays, they have an excellent and sharp dose-distribution that is superior to X-rays, and therefore can treat tumors more precisely with sparing surrounding normal structures, and they have a 2 to 3 times stronger biologic power to kill cancer cells than X-rays or protons so that they can more effectively control radiation-resistant tumors. Therefore, as an effective treatment that "cures cancer without compromising functional preservation through surgery" to provide more better QOL, Heavy ion therapy is preferable for radiation-resistant types of tumors such as those associated with liver cancer, malignant melanoma, bone and soft tissue sarcoma.

According to the results of treatment in clinical trials using carbon ion beam therapy for over 9000 patients, which were started in June 1994 at NIRS in Chiba Japan, at present, lung cancer, liver cancer, pancreatic cancer, head and neck cancer, prostate cancer, bone and soft tissue sarcoma and so on are expected to be good candidates

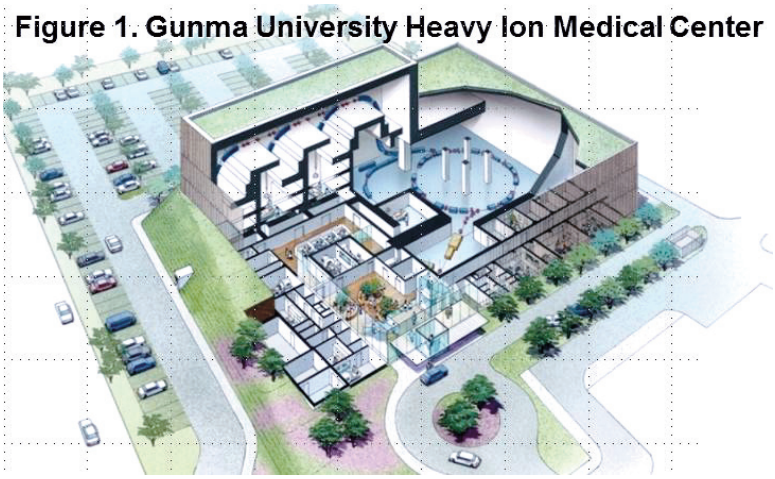
for heavy ion therapy. This achievement has been evaluated as one of the most important scientific and technological achievements in the 10-Year Strategy for Cancer Control, and the Japanese government has been promoting the distribution of particle beam therapy across the country.

Gunma University has promoted, with cooperation of NIRS in Chiba, the research and development of the compact heavy ion therapy facility and introduced the compact heavy ion therapy machine at Gunma University. In addition, with strong support from local governments such as Gunma Prefecture, Gunma University completed construction of its compact heavy ion therapy facility in 2008 and started utilizing heavy ion therapy for cancers with the compact heavy ion therapy facility in March 2010. As of end of 2014, more than 1500 patients with various cancers have been treated safely using this therapy. The present paper introduces the current status of heavy ion therapy at Gunma University and an outline of the Gunma heavy ion therapy project.

Outline of Gunma University heavy ion therapy facility

The heavy ion therapy facility designed for Gunma University is, as described, the practical and compact heavy ion therapy machine intended to deliver nation -widely **(Figure 1).**

Figure 1. Gunma University Heavy Ion Medical Center



In addition, it provides another specification for the research and development of a carbon ion micro-surgery system as an option. The dimensions of the building are approximately 65m x 45m x 20m, housed within it is the ion source generator, the first-step linear accelerator, the synchrotron, which is the main accelerator and about 20m in diameter, the beam transfer lines, and three treatment rooms plus one research and development room. The treatment rooms consist of one with a horizontal irradiation port, one with horizontal and vertical irradiation ports, and one with a vertical irradiation port, while the research and development room micro-surgery system. The total construction budget is about 13 billion yen. In addition, as treatment support functions for planning the patient's series of treatments, it has a treatment planning room, two CT simulation rooms, an MRI room, and a PET/CT room. In this facility, the beam used for treatment consists only of carbon ions. The accelerator's design produces the beam intensity required for irradiating an exposure field of 15cm x 15cm at 5GyE/minute in the case of standard treatment conditions. The carbon ion beam can be accelerated up to 400MeV for each nucleus, which can penetrate about 25cm into water, and can cover treatment for most deep cancers.

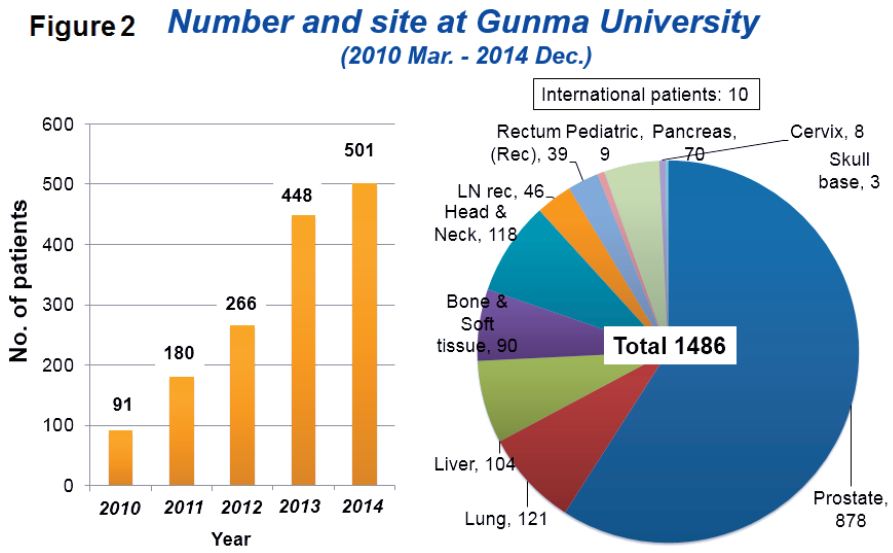
The beam is introduced into each irradiation chamber through the high energy beam transportation system, and tuned using various apparatus to form an irregular shaped dose distribution that encompasses the corresponding tumor. The passive broad beam delivery method is employed as a safe and easy method of forming the irradiation field. The narrow beam is expanded to a wide beam using the wobbler electromagnets and the scatterer, and a Spread Out Bragg Peak (SOBP) is created using the ridge filter system. A collimator and

Bolus are used to shape the dose distribution according to the patient's treatment area. The staking layer irradiation method is introduced into this beam line to improve the dose distribution of upstream edge of tumor for concentrating much more on the bulk of the tumor. The surrounding normal tissue can be much more spared from an unnecessary dose by dynamically moving the multi-leaf collimator and the range shifter in a coordinated fashion. In addition, the synchronous respiratory gating irradiation method, which matches the timing of irradiation to the patient's breath for the sake of internal organs that are adapted to the movement of the breath in order to improve the dose distribution on the tumor, and to decrease the side effects on normal tissue.

Clinical results of patients treated with heavy ion therapy

A total of 1,486 patients were treated with carbon beam therapy at GHMC from March 2010 up to end of 2014(**Figure 2**). Classified according to the site of the tumor, there were 878 prostate cancers, 121 lung cancers, 104 liver cancers, 118 head and neck cancers, 90 bone and soft tissue sarcomas, and 175 other cancers. Although the median follow-up period was short, about 2.5 years, and was not enough to assess the full scope of the outcomes, severe acute and chronic radiation reactions have not occurred thus far.

The early clinical results were analyzed for three diseases of relatively large numbers of patients treated such as prostate cancer, liver cancer and lung cancer as follows.



1. Prostate cancer:

A total of 304 patients were treated between 2010 and 2013. Median age of patients was 66 years-old and median follow up period was 30.1 months. According to risk group, the number of patients with low, intermediate, and high risk groups were 16, 142 and 146 patients which indicated 95 % of the patients were in Intermediate or high risk groups. Total dose of carbon irradiation was 57.6 Gy(RBE) in 16 fractions. Androgen deprivation therapy was delivered according to the risk groups. Basically, ADT was not used for low-risk group. Patients with Intermediate-risk were treated with neoadjuvant ADT for 6 months. For the high-risk patients, Adjuvant ADT was continued until 2 years. The patients with this group (PSA less than 10 ng/ml, a Gleason score of 3+4, and clinical stages T1c to T2b) were exceptionally treated without ADT. Patients treated without ADT were 22%.

2-year biochemical relapse free survival rate was 97.0%. Until now, biochemical failures occurred in 9

patients and no local failure and 4 distant metastases were observed. There were 2 deaths from the disease. There was no patient experienced with grade 3 or more toxicity in Gastrointestinal and genitourinary organs. Grade 2 toxicity were seen in only 1 patient (0.3%) for Gastrointestinal organs and 14 (4.6 %) for genitourinary organs. These incidences indicated the carbon beam therapy showed less radiation induced complications than photon and proton therapies in Gastrointestinal and genitourinary organs. The current prospective study demonstrated that carbon ion radiotherapy for prostate cancer was as safe as the previous report from NIRS.

2. Liver cancer:

A total of 55 patients with liver cancer whose PS status were PS 0:38, PS1:16, PS2:1, and Child Phgh score were C-P A:47 (85%), B:8 (15%), were treated with carbon beam therapy from 2010 to 2014. Median tumor diameter was 3.7cm ranging from 0.9-9.0cm and UICC-TNM were stage 1:40, stage 2:10, stage 3a:3, stage 3b:2. Median follow-up period was 22 months ranging from 7m to 48m. The 2year local control rate was 81.8% and the 2y over-all survival rate was 78.2%. There was no acute and late reaction greater than G2. Patients treated with 52.8Gy(RBE) with 4 fractions showed poorer local control rate of 80% in 2 years than the 100% of 60Gy(RBE).

3. Lung cancer:

A total of 53 patients with lung cancers including 36 patients with stage T1 and 17 patients with T2a and 21 with adenocarcinomas and 13 squamous cell carcinomas. Patients with stage T1 disease were treated with total dose of 52.8 Gy (RBE) in 13.2Gy(RBE)/fraction with 4 fractions, and patients with T2 disease were treated with total dose of 60Gy(RBE) in 15Gy(RBE)/fraction with 4 fraction. Respiratory gating method was utilized for respiratory movement of tumors.

Median follow-up period was 20 months. The 2year local control rate was 89% and aver all survival rate was 85%. Grade 2 and grade 3 pneumonitis (CTCAEv4) were observed for one and one patients, respectively, which represented about 4%.

Development of heavy-ion micro-surgery system at GHMC

The heavy ion therapy facility at Gunma University has a fourth treatment room for research and development. We are developing a high–precision heavy ion micro-surgery system in this room. The heavy ion micro-surgery system is a treatment technique for controlling the beam spot with a highly precise spatial position, on the order of millimeters, in order to take full advantage of the sharper and lower side scatter of carbon ions. High-precision heavy ion micro-surgery focuses a carbon beam down to a size of 1mm to 3mm φ, and can irradiate a minute targets in the body with the focused beam at a4 positional accuracy of less than 1mm, and thus treat the diseases. This technique is an innovative cutting-edge technique found nowhere else in the world, and we have already applied for a patent covering the principal elements of the method. This treatment technique can be extended to apply to the treatment of a variety of benign diseases other than cancers, such as vascular lesions and tumors adjacent to the spinal cord, pituitary tumors, acoustic neuromas, AVM, and age-related macular degeneration.

For those purposes, our group invented a novel beam focusing system, which uses a vertical irradiation port with 4 specialized focusing magnets to produce both a 0.4mm beam radius in 1-sigma size and 150mm square wide irradiation field with a positional accuracy of less than 1mm using a 3D spot scanning method.

Figure 3 represents the last 9m in the line of an irregular beam. With the conventional focusing system it is difficult to manage both the control of a small beam size and a wide irradiation field. The Gunma-type beam design is inspired by a "hadron collider", for example, the LHC at CERN. The collider strongly focuses a hadron beam and detects elementary particles with a huge detector, without using focusing magnets. In the Gunma design, the carbon beam size is expanded widely at first, and then strongly focused, in order to maintain its focus

even when the beam is transmitted through the human body. Our group discovered how to design the beam to manage both a 0.4mm beam radius in 1-sigma size and a 150mm square wide irradiation field.

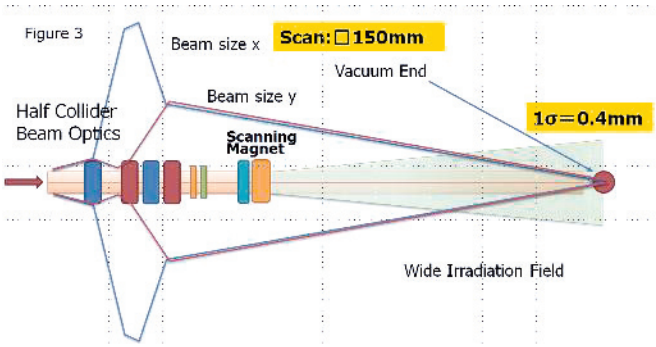
We have already achieved a 1σ = 1.4 mm wide beam spot. Beam depth control with 0.1mm precision is achieved by incorporating the air gap from the surface of the body in order to modulate faint beam penetration.

Beam depth control with a precision of 0.1mm is another task in sub-mm carbon beam surgery. In particular, the change in thickness of the range-shifter affects the beam size. We found that the air gap between the end of the range-shifter and the surface of the human body is appropriate for modulating small beam depth and size, because the density of the air is not zero but 1/1000 of water.

In addition, a sophisticated beam-range-control system was developed for treating age-related macular degeneration. The pretreatment scanning Bragg peak of carbons was used as the excitation light for fluorescence from the Indocianine green that accumulates in the lesion in order to set the penetration level of the beams accurately by determining the energy that generates the maximum fluorescence from the lesion.

Moreover, a CdTe Compton camera was developed to measure the gamma rays that scatter from the carbon ions in order to verify the exact beam positioning. We developed a three-dimensional image of multi-RI distributions and successfully obtained simultaneous images of two RIs administered to rats and confirmed the potential energy to be from at least Tc-99m γ-rays up to F-18 γ-rays.

The clinical experiment with carbon ion micro-surgery will be initiated with small beam spots of 2-3mm for a variety of diseases by 2018.



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Status Report of the Italian National Center for Oncologic Hadrontherapy

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Abstract

The Italian Center for Oncologic Hadrontherapy is up to date in the fifth year of its clinical activity. The total number of patients treated is 685 (up to November 2015). The treatments with carbon ions are about three times those with protons. An important part of treatments with carbon ions is directed on sarcomas, bones and soft tissue sarcomas, salivary glands tumours. In the table, treated patients are listed according to the clinical trials approved by the Italian Ministry of Health.

Another substantial part of treatments regards re-irradiation of several pathologies, especially head and neck re-treatments of several tumours.

An important goal reached in the last year is the treatment of moving targets. Pancreatic adenocarcinomas, hepatocellar carcinomas and pathologies located in moving sites are treated through the vertical beam line with gating and rescanning technology.

Treated volumes' issue has been discussed. Many pelvic sarcomas and chordomas cases refer to hadrontherapy treatment when already reached remarkable volumes. These cases are subject of discussion amongst radiation oncologists and medical physicists. The parameters taken in consideration are PTV (Planning Treatment Volume) and GTV (Gross Tumour Volume). They are statistically evaluated to elaborate the best treatment strategy in term of dose and planning option. This issue has also economic implications. The treatment of major tumour volumes using mostly more than one field occupies the treatment room for a period of time equal, when not superior, to two or more patients. The next challenge is to improve all steps to give such treatments in less time.

Most of the patients treated at CNAO are referred from Italian Cancer institutes but an increasing number of EU patients come to Pavia through international agreements.

In the coming period CNAO is expected to receive the authorization to treat all the clinical case worth to receive hadrontherapy treatment.

Clinical study description	Particle	Total number of patients treated
Proton radiation therapy for chordomas and chondrosarcomas of the skull base	Protons	52
Proton therapy of spine chordoma and chondrosarcoma (amended)	Protons	16
Proton therapy of intracranial meningioma	Protons	24
Proton therapy of brain tumors	Protons	11
Proton therapy of recurrent cervico-cephalic area tumors	Protons	21
Proton boost for locally advanced cervico-cephalic area tumors (amended)	Protons	28
Proton therapy of glioblastoma	Protons	1
Proton re-irradiation of recurrent spine chordoma and chondrosarcoma	Protons	6
Carbon ion therapy of adenoid cystic carcinoma of salivary glands (amended)	Carbon ions	106
Carbon ion re-irradiation of recurrent pleomorphic adenomas	Carbon ions	19
Carbon ion re-irradiation of recurrent rectal cancer	Carbon ions	8
Carbon ion radiotherapy for bone and soft tissue sarcoma of cervico-cephalic area	Carbon ions	94
Carbon ion radiotherapy for bone and soft tissue sarcoma of trunk	Carbon ions	119
Carbon ion therapy of recurrent cervico-cephalic area tumors	Carbon ions	90
Carbon ion therapy of malignant melanoma of the mucous of the upper aerodigestive tract	Carbon ions	14
Carbon ion therapy for high risk prostate cancer	Carbon ions	9
Carbon ion therapy of primary and secondary orbital tumors	Carbon ions	13
Carbon ion therapy for pancreatic cancers	Carbon ions	11
Carbon ions therapy of primary malignant tumors of the liver	Carbon ions	4
Carbon ion re-irradiation of recurrent spinal chordoma and chondrosarcoma	Carbon ions	7
Protons and/or carbon ion integrated radiotherapy for poor prognosis in patients with inoperable sinonasal tumor	Protons/ Carbon ions	4
Other	-	28
		685

Status Report of SAGA-HIMAT

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1. Construction and specifications of SAGA HIMAT

SAGA HIMAT is the fourth carbon ion beam therapy facility in Japan. SAGA HIMAT stands for Saga Heavy Ion Medical Accelerator in Tosu. It is located in Tosu city, Saga prefecture (Fig.1). SAGA HIMAT Project is a collaborative work among the local (Saga prefectural, Fukuoka prefectural and Tosu city, and Kurume city) governments, regional industries, and medical societies in Kyushu area. The initial cost was about 15 billion yen which was covered by donations, investments, finances, and some by aids from local governments. It is managed by non-profit SAGA HIMAT Foundation.

Fig. 1 SAGA HIMAT（left） is close to Shin-Tosu station（right） which is at the cross-point of Kyushu-Shinkansen and Nagasaki-Honsen railways

The construction of the building and the accelerators took a year and eight months. Then, the acceptance tests took eight months and the commissioning tests for the prostate cancers two months. We opened the clinic in June 2013, and started treatment of prostatic cancers in August 2013, while continuing the acceptance tests for other organ cancers.

At SAGA HIMAT, carbon ions are accelerated by two linear accelerators and a synchrotron up to 70% of light speed, and they are transported to the treatment rooms A and B where broad beams are used. The range of extracted energy is 140–400MeV/u (Fig.2, Table 1). The room A has horizontal and 45 degree oblique and the room B has horizontal and vertical beam lines, and each outlet of the beams measures 15x15cm^2. As preparations for treatment, the radiation technologists make an immobilization device adjusted to the patient placed on a mock treatment couch. Dose compensation boluses adjusted to the shape of the irradiation fields are designed from the CT simulation data and produced by outside manufactures. We also have a regular CT scanner and MRI for diagnosis.

The treatment room C has horizontal and vertical beam lines and is now under preparation for pencil beam scanning therapy which will be ready in April 2017. The maximum irradiation field will be 22x22cm^2.

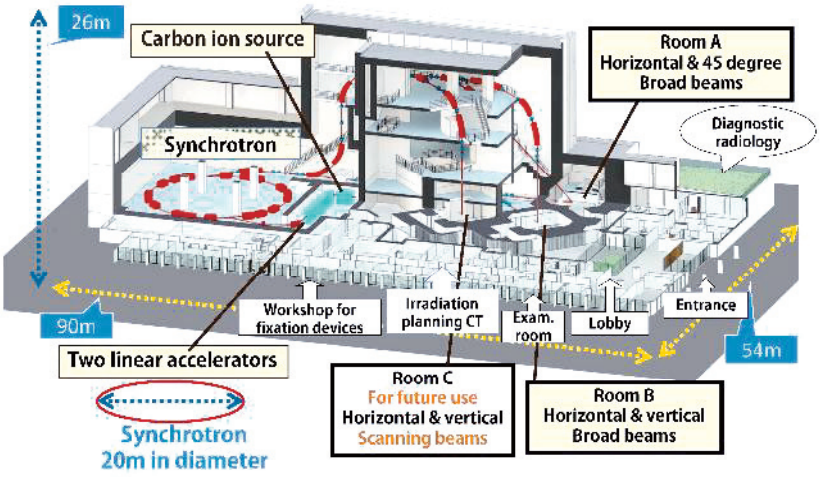

Fig 2. Facility layout of SAGA HIMAT

Table 1. Specifications of SAGA HIMAT

Ion species	^{12}C
Ion source	ECR IS
Injector linacs	RFQ, 0.6MeV/u APF-IH, 4MeV/u
Synchrotron	Circumference 61.5m
Extracted energy	140-400MeV/u
Beam intensity	$1.0x10^{9}$pps
Irradiation size	$15x15cm^2$ (broad beams in room A and B) $22x22cm^2$ (scanning beams in room C)
Treatment rooms	A (horizontal and 45 degree oblique broad beams) B (horizontal and vertical broad beams) C (horizontal and vertical scanning beams to be ready in April 2017)

2. Clinical system at SAGA HIMAT

SAGA HIMAT is a standalone outpatient clinic specialized for carbon ion cancer therapy. The patients initially visit a cancer treatment facility of their choice, get diagnosis and staging of the cancer and will be referred to our place for carbon ion therapy. We do not have beds. All are treated as out-patients. If necessary, small number of the patients may be admitted to nearby affiliated hospitals and commute to SAGA HIMAT for the carbon ion therapy. After completion of the therapy, the patients will be observed regularly both at our clinic and at the original institute.

Our medical staff includes five radiation oncologists, one diagnostic radiologist, four medical physicists, ten radiology technologists, and seven nurses. The accelerator operators (six people) are outsourced. Many of the medical staff was trained at National Institute of Radiological Sciences (NIRS) in Chiba or at Gunma University from 3 months to 3 years. The radiology departments of three nearby university hospitals, Saga, Kurume, and Kyushu are particularly committed to the project. They train and provide the medical staff to SAGA HIMAT. They also have ion beam therapy consultation clinics and select the patients for carbon ion therapy and send

them to SAGA HIMAT. In order to perform the patient referral and treatment smoothly, we exchanged medical agreements with many institutes, including 10 university hospitals and many major cancer institutions in Kyushu area. The population of Kyushu area is about 13 millions.

Our treatment protocols are mainly based on those of NIRS. Furthermore, clinical review boards for 9 different organs (1.urological, 2.head and neck, 3.lung and mediastinum, 4.liver, 5.pancreas, 6.bone and soft tissue, 7.recurrent rectal, 8.esophageal, 9.gynecological tumors) were made to check and discuss our treatment protocols and the clinical results. The board members consist of cancer authorities including surgeons, medical oncologists, radiation oncologists, pathologists, and statistics professionals from outside facilities. They also help patient referral and advise us on designing the clinical studies.

3. Initial results and future plans of SAGA HIMAT

We started treatment of prostatic cancers in August 2013, then, treatment of head and neck cancers and bone and soft tissue tumors started in December 2013, and respiratory gated treatment for lung, liver, and pancreas cancers in March 2014. By the end of October 2015, we had treated 1,029 patients, including 696 prostatic, 92 liver, 79 lung, 52 head and neck, 59 pancreatic, 21 bone and soft tissue, 3 renal and 10 local recurrent rectal cancers and 17 other cancers. Since the opening of the clinic, the operation of the accelerators were rather stable and patient treatments stopped in a little less than two days, mainly because of electric power troubles.

We are now preparing for the treatment protocols of esophageal and gynecological cancers. The treatment room C will be ready for pencil beam scanning therapy in April 2017. Then, we plan to treat over 800 patients a year in near future. We are also making preparations to accept patients from foreign countries. We hope carbon ion therapy will become one of the major choices to treat cancer patients and SAGA HIMAT will become a model case of multi-facility collaboration for cancer treatment.

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Website http://133.242.195.62/ SAGA HIMAT Top Page

Status Report of SPHIC

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The Shanghai Proton and Heavy Ion Center (SPHIC) is an academic center specialized in radiation therapy. It is equipped with the IONTRIS proton and carbon ion radiation therapy facility. In addition, the hospital is also equipped with two Varian TrueBeam photon therapy systems. Before the clinical application, it is required by the Chinese FDA that a registration trial must be successfully completed to confirm the safety of the IONTRIS facility in Chinese patients. Therefore, the hospital started its phase II registration trial (the "IONTRIS" trial) in June 2014, and completed the study treatment in late December 2014. The hospital was approved by the Chinese FDA for patient care in March 2015 after the successful completion of the clinical trial.

The one-year results of the IONTRIS Trial

A total of 35 patients were accrued in the IONTRIS trial. Nineteen, 10, 4, 1 and 1 patients have prostate, head and neck, pulmonary, liver and abdominal sarcoma respectively. Twenty-two patients received carbon-ion radiotherapy (CIRT) and the rest had proton therapy. All patients have achieved SD, PR, or CR after the radiation therapy. As required by the registration trail, all the patients must be closely followed up by the hospital every 3 months. So far all patients are under follow-up and no patient has lost in follow-up.

The 12-month overall survival was 100%, and the progression-free survival was 97.1%. Only one patient with colon cancer with lung metastasis might have local progression in the pulmonary foci. The lesions achieved partial response but slightly enlarged after 9 months. However, at this time the lesions irradiated are all at stable status. Overall, we consider the outcome of the trial favorable at this time.

Current practice at SPHIC including clinical research

SPHIC started routine patient care in May 2015. By the end of November 2015 we have treated approximately 160 patients and the majority received carbon therapy. Disease treated include chordoma, nasopharyngeal cancer, adenoid cystic carcinoma, oral/oropharyngeal cancer, liver cancer, pancreatic cancer, prostate cancer, sarcoma, lung cancer, and several other conditions.

We consider clinical research as an important integral part of our practice, thus have already initiated a number of trials. Here I used head and neck as an example. The current focus of our head/neck research is re-irradiation using carbon-ion for locally recurrent nasopharyngeal cancer (NPC) since we consider recurrent NPC after IMXT is resistant to another course of photon therapy. And the physical and biological features of particle therapy can benefit this group of patients over IMXT. Other trials being planned in head/neck cancer including randomized trials to compare the effectiveness of CIRT versus proton in chordoma and GBM.

Challenges in the treatment of head/neck cancer with CIRT including the uncertainties in the optimal dose/fractionation for different pathologies. The outcome from our NPC re-CIRT protocol may not be applicable to other pathologies such as SCC and sarcoma. Clinical trials may answer some of the important questions that we have on CIRT, but the mechanism of the improved efficacy will need the support from translational studies and basic research.

Status Report of i-ROCK (Kanagawa)

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Abstract

The ion-beam Radiation Oncology Center in Kanagawa (i-ROCK) is the carbon ion radiation therapy facility at the Kanagawa Cancer Center (KCC). The KCC is located in Yokohama City, capital of Kanagawa Prefecture. Our facility's most distinguishing advantage lies in its ideal location for receiving outpatients from local and regional areas. All of KCC's staff are specialists in cancer care. We will be able to offer a full range of treatment options and high-level services to patients with any type of cancer. One characteristic of i-ROCK is that each treatment room has on-rail in-room computed tomography. We will start carbon ion radiation therapy using spot scanning method, and i-ROCK will be the first specialized facility for the scanning method of carbon ion radiation therapy in Japan. The start of clinical operation is planned for December 2015.

Introduction

The Kanagawa Cancer Center (KCC) is the core facility for cancer care in Kanagawa Prefecture. It serves a population of over 9 million people. Planning for the ion-beam Radiation Oncology Center in Kanagawa (i-ROCK) started in 2005, and the basic framework and design of i-ROCK was established in 2010. i-ROCK is the first cancer-center-based carbon-ion radiotherapy facility in the world. The building was completed in August 2014. The installation of beam delivery equipment has been completed. The start of clinical operation is planned for December 2015. The current status of i-ROCK is presented in this report.

Clinical

Our facility's most distinguishing advantage lies in its location. The KCC is located in Yokohama City, capital of Kanagawa Prefecture, and one of the largest metropolitan areas in Japan. The population is 3.7 million in the city and 9.1 million in the prefecture. Our facility also has a regional advantage as it covers half of the greater Tokyo metropolitan area, which encompasses nearly 50 million people, as well as other surrounding prefectures. These areas are all within 1 hour by public transport. Thus, KCC stands at an ideal location for receiving outpatients from local and regional areas.

All of KCC's staff are specialists in cancer care. The protocols and treatment plans, including surgery, chemotherapy, radiation therapy, and their combination, are determined at a cancer board meeting, which is routinely held for each specific cancer. We will be able to offer a full range of treatment options and high-level services to patients with any type and stage of cancer.

The Department of Radiation Oncology currently operates 4 linear accelerators and has an image-guided brachytherapy system with an in-room computed tomography scanner. Thus, we will be able to provide carbon ion radiation therapy and precise photon radiation therapy, to any kind of cancer patient.

Outline of Facilities

After discussion of the conceptual design of the role of carbon ion radiotherapy in a cancer center, KCC contracted with Toshiba Corporation in 2012 to produce the system. i-ROCK is a compact carbon ion facility for widespread use designed by the Japanese National Institute of Radiological Sciences.

The facility is based on a synchrotron accelerator that feeds 4 treatment rooms (Fig. 1). The treatment rooms have fixed beam ports, 2 rooms with horizontal and vertical beam ports, another 2 rooms with horizontal beam port. We adopt a pencil beam 3-dimentional scanning method for beam shaping of irradiation field. Maximum energy is 430 MeV/n, then residual range is more than 25 cm in water. Beam range is controlled by fine-range shifters with multistep variable energy (11 steps). Treatment couch at each room is robotic couch with 7 degrees of freedom. For patient positioning, we use Orthogonal X-ray FPD (flat panel detector) imaging system.

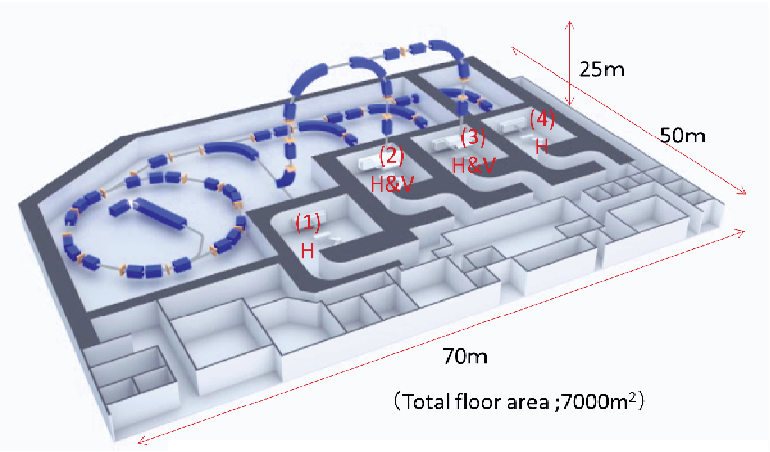

Fig. 1 Bird's eye view floor plan of i-ROCK

The treatment planning system was developed on the Monaco (Elekta) platform with algorithms for carbon ion dose calculation and pencil beam scanning optimization developed by the Japanese National Institute of Radiological Sciences. One characteristic of i-ROCK is that each treatment room has on-rail in-room computed tomography, allowing for verification of the internal target volume and critical organ position based on the calculated dose distribution (Fig. 2).


Fig. 2 Treatment room with a robotic couch and in-room CT

We succeeded in accelerating the carbon ion beam to maximum output energy in January 2015. In February 2015, we achieved an 11-step energy and scanning control of the pencil beam. In the same month the facility passed the government safety inspection for particle radiation therapy facilities.

Current Status

We will start carbon ion radiation therapy using spot scanning method, and i-ROCK will be the first specialized facility for the scanning method of carbon ion radiation therapy in Japan. And soon, we are going to start a clinical trial to apply for advanced medical care approved by Ministry of Health, Labour and Welfare.

Status Report of Carbon Ion Radiotherapy Facility at Yamagata University

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Abstract

After more than 10 years' effort to establish the first heavy ion radiotherapy facility in Tohoku region, our project is now entering a construction phase that will end in 2019. Distinctive features of our facility are the annexable smaller building area, environment-friendliness and easier management that will eventually become the world standard of the heavy ion therapy facility. We are installing two treatment rooms; one has fixed beam ports and the other has a 360˚ rotating gantry with superconducting magnets. We completely employ active beam scanning rather than passive beam shaping. We plan to treat the first patient in autumn 2019.

Introduction

Heavy ion radiotherapy, especially carbon-ion radiotherapy, is known to have many advantages in principle such as higher relative biological effectiveness (RBE), excellent dose distribution, small lateral scattering, oxygen-insensitiveness, fewer hypofractionation [1]. However, the availability of heavy ion radiotherapy is very limited worldwide. One major reason is that the heavy ion radiotherapy requires a state-of-the-art, large-scaled, and very expensive facility. Another reason is the immature clinical evidence of the superiority to other radiotherapy such as intensity modulated radiotherapy (IMRT) or proton therapy.

Since we intend to resolve these two major difficulties in spreading of the heavy ion radiotherapy worldwide, we have been planning a new conceptual heavy ion radiotherapy facility for more than ten years. The concept is "eco-friendly and annexable to existing hospital". In order to realize the concept, we set four main features for our facility: 1) smaller building area annexable to the existing hospital, 2) less energy consumption, 3) easy management, 4) reduced wastes. After 3 years' R&D period, our budget request for facility construction to Ministry of Education, Culture, Sports, Science and Technology (MEXT) is eventually approved in January 2015. Although this national budget does not cover whole expense at installation, thanks to great financial supports from municipal governments around and many individuals, we have just began our facility installation project officially that will last until 2019. This will be the first heavy ion radiotherapy facility in northern Japan that has population of 14 million. Through the operation, we will demonstrate not only the excellence of our facility, but also the additional clinical evidences of carbon-ion radiotherapy compared with IMRT and proton therapy.

In this paper, we present the features and the current status of our project.

Facility Concept

As mentioned above, our facility concept is oriented toward the global market. Significant problems related to the new installation of the existing carbon-ion radiotherapy system are as follows: their large scale, huge installation cost, high running cost, requirement of high-level operation personnel, patient-specific disposal

(collimators and compensators) with modest radioactivity, etc. Although it is difficult to reduce the high installation cost significantly, the other problems can be resolved by recent technical progresses.

1. Small Building Area

Initial heavy ion radiotherapy facilities such as HIMAC and HIBMC have large building area, typically comparable to the size of football pitch (~7500 m^2). This size requirement is clearly an obstacle to construction, especially for urban hospitals. Then it was reduced to 3140 m^2 at GHMC with a new compact synchrotron optimized for carbon ion radiotherapy [2]. We plan to reduce it further, even to ~2000m^2. For realizing this, we configure the main accelerator and treatment rooms on different floor levels. The main accelerator (synchrotron) is installed on the basement floor, and treatment rooms are on the 2nd floor where a bridge to the main hospital is connected. Patients and medical staffs can access the facility easily via the connecting bridge. The 3D image of the building is shown in Fig.1. (This design is not finalized yet.)

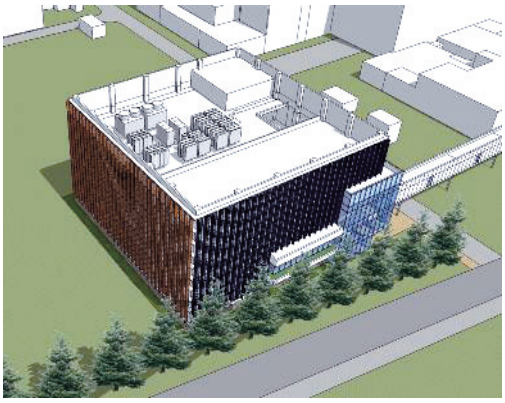

Fig.1. Image view of the building of the heavy-ion radiotherapy facility (not final design).

2. Energy-saving

Heavy ion radiotherapy facility is known to consume massive electrical energy at operation. The main consumer is of course the synchrotron, of which the bending magnets consume ~1MW on average at full power operation of the existing synchrotrons for carbon-ion radiotherapy. We are going to reduce this energy consumption by several methods including on-demand operation and newly-designed magnets. In addition, we will employ slower acceleration and extended flattop pattern to reduce peak power, which can lower the demand charge and the requirement for the electrical equipment including transformers. By these attempts, yearly electric charge is expected to drop to half of that for the current facilities.

3. Easy Management

Since the heavy ion radiotherapy system employs state-of-the-art technologies, a number of experts are required at operation and maintenance works, which raises the running cost. In order to suppress this cost and make the facility easier to use, we are going to take several measures including the automatic beam positioning system and remote monitoring system. In addition, we are considering to apply solid-state RF power amplifiers in place of the current tetrode vacuum-tube amplifiers to avoid the periodical (maybe yearly) replacement work.

4. Reduced Wastes

Although passive beam shaping has more clinical experiences than active beam scanning, it uses costly patient-specific collimator and compensator for beam shaping to become wastes with modest radioactivity. We plan to completely abandon the passive beam scanning to reduce the running cost and nullify such wastes. The active beam scanning system, developed by NIRS [3], will be installed and it will eventually realize the better dose distribution than the passive beam shaping.

Facility Overview

As mentioned above, we separate the floors of the main accelerator and treatment rooms. On the basement floor, an injector and a synchrotron are installed. The injector, which is similar to the prior facilities, is located inside the synchrotron ring to save the floor space. Although some minor changes might be applied, the

synchrotron ring itself is similar to the prior facilities whose diameter is ~20 m. Its maximum energy is 430 MeV/u. After carbon beam is horizontally ejected from the synchrotron, it will be bent upward to the upper floor where the treatment rooms are located. On the ground level floor, power supplies mainly for the synchrotron are installed.

Treatment rooms are located on the 2nd floor. There are two treatment rooms: a fixed port room and a rotating gantry room. A horizontal and a vertical port will be installed in the fixed port room. After the first 360° rotating gantry with superconducting magnets for carbon ion radiotherapy has been developed by NIRS [4], a modified version of it will be installed in the gantry room. A robotic-armed bed with X-ray positioning system is equipped at each treatment room. Modalities such as CT and MRI for radiotherapy treatment planning (RTP) are installed on the same floor. Consulting rooms, reception, waiting space and operation room are also installed on the 2nd floor. Rooms for medical and technical staffs as well as a conference room and an RTP room are located on the 3rd floor. Necessary power supplies are also installed on the 3rd floor. On the 4th floor, utilities are equipped, and the vertical beam line will pass through the floor. Total floor area will be approximately 7300 m^2. Configuration of the main components are shown in Fig.2.

Fig.2. Configuration of main components (Courtesy of Toshiba).

Installation Plan

Our overall schedule until first treatment is shown in Fig. 3. After a few years' R&D on the facility concept described above, we are making the basic architectural design with Nihon Sekkei, Inc.. After the design work, building construction will start in 2016 and end in 2018. We contracted with TOSHIBA for the installation of the heavy ion radiotherapy system in September 2015 through a proposal competition. They will install the whole system until the end of FY2018 according to the contract. We will carry out the commissioning work with the help of TOSHIBA after the system installation, and then we will begin treatment in October 2019.

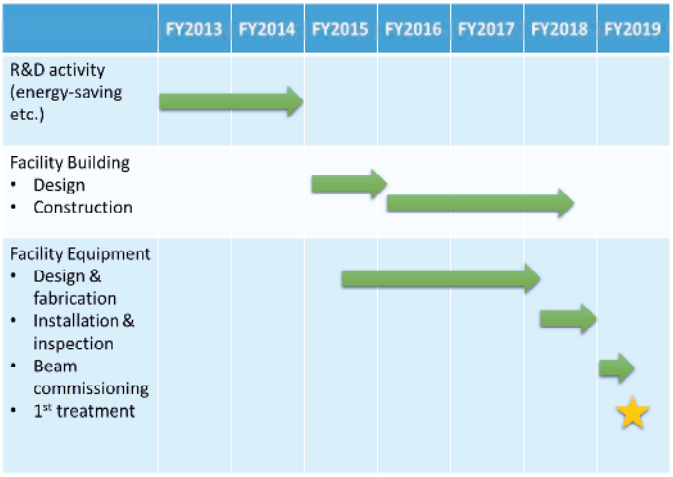

Fig.3 Schedule until first treatment.

Summary

Yamagata University Faculty of Medicine has been planning the first heavy ion radiotherapy facility in Tohoku region for more than ten years. By the financial support of the national government, municipal governments, local companies and individuals, we have just started the building construction and system fabrication processes. Our facility is space-saving, energy-saving, easily manageable and few wastes, which is developed as an annexable option to the existing hospital. It has two treatment rooms: a fixed-port room and a 360° gantry room with state-of-the-art superconducting magnets. We are aiming to begin treatment in October 2019.

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Acknowledgment

The authors wish to thank the experts of the physics division of NIRS for their help to the planning of our heavy ion radiotherapy system. We also thank staff members of R&D office for heavy ion radiotherapy system for their extensive efforts. We thank TOSHIBA Corporation for their effort to bring our facility concept into reality, and also NIHON SEKKEI, INC. for their architectural design works. And above all, we wish to thank all the financial support from national and municipal governments, and especially private companies and generous individuals.

Current Status of Carbon-Ion Radiotherapy Facility at Osaka

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Abstract

Introduction

Osaka is the largest city in Western Japan, and it has a population of 8.8 million. Unfortunately, death rates from cancer are high in Osaka district. Therefore, it is important to decrease mortality rates from cancer.

Methods and Materials

From September 2018, carbon-ion radiotherapy facility will be open at Osaka City. The site of this facility is very close to Osaka Castle.

Results

This facility has three treatment rooms, and scanning beam will be employed at all 3 treatment rooms. This facility will be available for more than 800 patients per year

Discussion

This facility will have close associations with University hospitals in Osaka district, associated hospitals and Osaka cancer centers regarding cares for cancer patients. This facility will help improve the cares for cancer patients, especially those who had advanced and/or refractory cancers.

Conclusion

Carbon-ion radiotherapy is going to be started in Osaka from 2018.

Current Status of MedAustron

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

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

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

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

Current Status of KHIMA Project

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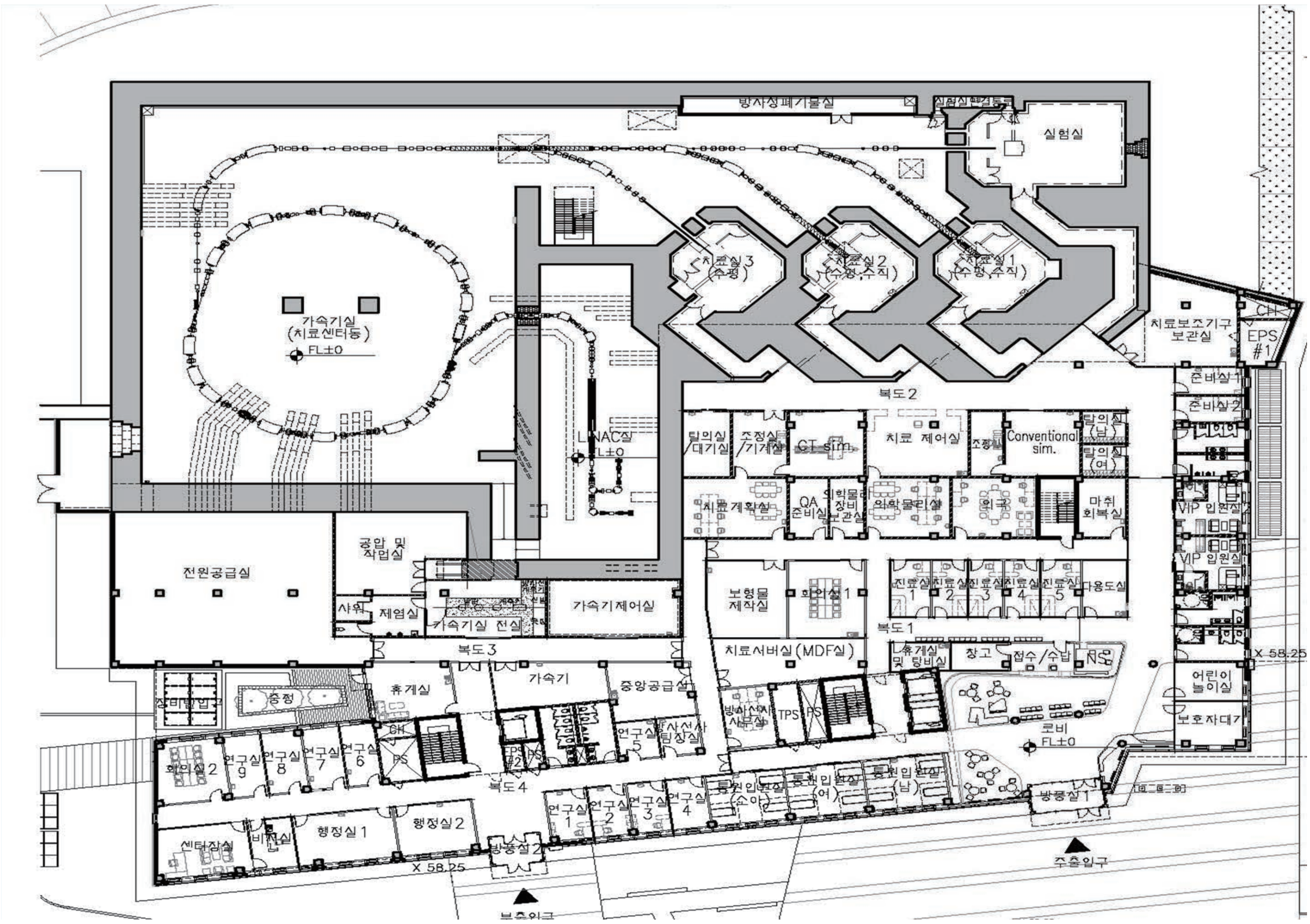
KHIMA project started from 2010, and now is constructing heavy ion particle therapy system, which includes a synchrotron generating a carbon of 430 MeV and proton of 230 MeV beams, 3 treatment rooms with horizontal and vertical beams, and pencil beam scanning. The location of KHIMA is Busan city in Korea, where is Korea's 2nd largest city with a population of about 3.5 million. The building of KHIMA is located close by Dongnam Institute of Radiological & Medical Sciences, which is a branch hospital of KIRAMS. The building construction would be completed at April 2016. Now we are getting ready for manufacture, installation, assembly of accelerator and treatment system to finish as scheduled by December 2017. Several research project and biological experiments for radiosensitizer candidate of carbon beam have been done with cooperation of NIRS.

Period	2013. November ~ 2016. April
Location	Busan Metropolitan City, Gijang County
Plottage	88,139㎡ (Building : 82,006㎡, Road : 6,133㎡)
Building Area	Total Floor area : 18,352㎡ (Therapy Building: 13,422㎡, Research Building : 4,930㎡)
Scale of Building	2 ground levels and 2 underground levels

Heavy Ion Therapy Center (B


방사성폐기물실
실험실
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치료실2 (수평,수직)
치료실1 (수평,수직)
가속기실 (치료센터동)
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치료보조기구 보관실
EPS #1
복도2
탈의실 /대기실
조정실 /기계실
CT sim.
치료 제어실
Conventional sim.
탈의실 (남)
탈의실 (여)
치료계획실
QA 준비실
의학물리장비 보관실
의학물리실
마취 회복실
준비실1
준비실2
VIP 입원실
전원공급실
공압 및 작업실
가속기제어실
샤워
제염실
가속기실 전실
복도3
보형물 제작실
회의실1
진료실 1
진료실 2
진료실 3
진료실 4
진료실 5
다용도실
복도1
치료서버실(MDF실)
휴게실 및 탕비실
창고
접수/수납
NS
X 58.25
어린이 놀이실
보호자대기
로비 FL±0
휴게실
가속기
중앙공급실
중정
회의실2
연구실 9
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연구실 7
연구실 6
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주출입구

Planning the Heavy Ion Therapy and Research Facility in Dallas, Texas.

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Abstract

The first US hospital based heavy ion therapy and research center is being conceptually designed by the UT Southwestern Medical Center (UTSW) in Dallas, TX, USA. . UT Southwestern was recently awarded a two year planning grant by NCI to plan the research component of this initiative. We are actively assessing the technological capabilities of commercial systems available on the market to find out if they meet our clinical and research needs. The heavy ion system will be an integral part of a large unified complex with our conventional irradiation facility expansion. It includes seven conventional linear accelerators for patient care installed in the first stage and additional six conventional linacs installed in the second stage. The conventional phase has completed its architectural design and the first patient is expected to be treated in late 2016. This unified complex of all currently available modalities for radiation therapy will be located at the heart of the Dallas metroplex as an integral part of the UTSW medical complex, located only a couple of minutes from Dallas downtown. The heavy ion center is envisioned to have an accelerator accelerating ions up to $^{36}Ar^{18+}$ for energies equivalent to 430MeV/u for $^{12}C^{6+}$ ions. The center will include two clinical treatment rooms and one non-clinical research bunker with a fixed (non-gantry type) beam. The clinical treatment rooms will have pencil beam scanning capability. The proposed medical complex will serve as a national research and resource center where leading clinical, radiobiological and physics research will be conducted.

Introduction

UT Southwestern Medical Center (UTSW) is located in Dallas, Texas, USA. It is one of the largest medical schools in the US. In addition to its patient care and education mission, UTSW has a strong focus on medical research driven by more than 1000 faculty members, 6 of which are Nobel Prize laureates and more than 20 National Academy of Science members. The radiation oncology department at UTSW has been constantly expanding its conventional radiation services to keep up with the growing demand for its services due to the growth of the population and growth of market share. UTSW is constantly acquiring the latest technology available on the world market to provide the highest quality of cancer care to patients. In conjunction with this modernizing approach, UTSW has entered the planning phase to build the first hospital based heavy ion therapy and research center in the United States. The United States pioneered the usage of protons and heavier ions for cancer treatment. The first proton patient in the world was treated in 1954 at the Berkeley National Laboratory (LBNL). Two decades later the BEVALAC system at LBNL became primarily available for nuclear physics research. It was able to accelerate ions heavier than protons to therapeutic energies and used to treat patients. The program was closed in 1993 and the technology was exported and further developed in Asia and Europe. Until now, the US has been unable to bring this modality back to the US.

Overall Goal for the Heavy Ion Center

Our intent at UTSW is to create a synergistic system in which conventional and heavy ion clinical and research efforts are carried out under the umbrella of a powerful academic institution. Since our heavy ion center

will most likely be the first built after the BEVALAC shutdown, our intent is to develop a clinical system that serves as a national resource center while serving as a national research center.

Clinical goals: UTSW has a pool of world class clinicians and clinical scientists treating patients with stereotactic ablative radiation therapy (SABR) approach with conventional radiation modality and hypofractionated regimes. We are planning to build a heavy ion system with technical capabilities in line with our SABR effort. Our planned system will be capable of efficiently, precisely and safely deliver heavy ion beams in hypofractionted regimes, in addition to the standard techniques currently in use worldwide. We initially plan on developing a clinical system to irradiate about 1000 patients per year when running at full capacity. Furthermore, we are planning for a modular system capable of expanding its services beyond 1000 patients if the demand increases in the future. In addition, the system modularity will be such, that we will be able to install technological breakthrough results in accelerator and beam delivery systems expected to rise in the next two decades.

Research goals: Our major goal in building the heavy ion research center is to conduct carefully designed clinical trials to fully exploit the advantages of heavy ion therapy. The system will facilitate efficient and large scale clinical data generation, collection and analysis. Clinical and preclinical research efforts will be supported by physics and radiation biology research efforts.

Our goal is to setup a system with an infrastructure that will accommodate the research needs of physicists to create i) fast and precise dose engines; ii) range verification tools; iii) in vivo dosimetry tools; iv) motion management tools; v) adaptive re-planning tools and vi) fast and precise QA tools and vii) other physics tools vital for safe and precise clinical dose delivery. In addition to physics efforts directly related to clinical applications, we envision a system that supports research experiments related to the needs of extraterrestrial space travel and aerospace industries.

Furthermore, radiobiological experiments will be carried out to address topics related to the biological effectiveness of heavy ions in cell culture and in-vivo (small and large animals). The capabilities of our planned system will enable the evaluation of tumor and healthy tissues responses following exposure to heavy ion irradiation. We are also planning the development of radio protectors and radio sensitizers for heavy ion therapy. Besides research efforts related to cancer therapy, our system will host radiation biology experiments to study tissue effects upon immersion in radiation fields encountered during extraterrestrial travels beyond the protective magnetic zone of Earth.

Proposed Layout and Preliminary Specifications

To achieve the above stated research and clinical goals, UT Southwestern is planning to build an approximately 90 000 m^2 heavy ion facility adjacent to our conventional facility clinic. The heavy ion accelerator technology is envisioned to be a synchrotron tuned to accelerate charged particles with the charge to mass ratio Q/M= ½ to maximum initial kinetic energy equivalent to the 430MeV/u for $^{12}C^{6+}$ ions. We envision multiple ion sources serving the accelerator complex. Two clinical sources and one ion source that will be dedicated to research activities. The heaviest ion to be accelerated for physics and radiation biology research is $^{36}Ar^{18+}$. The heaviest ion envisioned for clinical research related to hypoxic tumors is $^{20}Ne^{10+}$. Our system will include two clinical treatment rooms equipped with compact superconducting (SC) heavy ion rotating gantries if the technology is accessible by the time of UTSW system installation. If the compact SC gantry is not clinically available, treatment rooms equipped with fixed beams will be installed the gantries will be considered in the expansion phase. The clinical rooms will be equipped with active pencil beam scanning delivery systems. The synchrotron is planned to deliver and tightly control high beam intensities needed to perform fast hypo-fractionated treatments. At the same time, low intensities are needed for gated repainting of tumors should that be the choice for moving target motion management. The treatment rooms should have enough space to perform range verification, patient setup and in vivo dose verification. In addition to the two clinical treatment

rooms, we are planning to build one dedicated research and quality assurance irradiation room equipped with a universal nozzle to allow both active scanned and passive scattered beams. The heavy ion system will have multiple modes of operations, such as clinical mode, QA mode and research mode. The difference between these modes is the degree of freedom a user will have to change the machine parameters.

Recent Progress

The lack of radiation therapy using charged particles heavier than a proton in the US was recently noticed by the government. The National Cancer Institute (NCI), one of the institutes of the US National Institutes of Health (NIH), awarded our institution a P20 planning grant to "encourage and support planning efforts for establishing a Center for Particle Beam Radiation Therapy (PBRT) Research. The Center must be planned to operate as a research center adjunct to an independently created and funded, sustainable clinical facility for PBRT. Ultimately, the proposed Center is expected to perform clinically relevant research using proton and heavier ion beams (including but not necessarily limited to carbon beams). The goal of this funding opportunity announcement is to provide the awardees with funding to enable inclusion of necessary resources (expertise or facilities) to carry out basic, and translational, and clinical research complementary to a clinical PBRT facility." UTSW applied for the opportunity and was awarded one of the two available grants in early 2015. The grant will span 2015 to 2017. As part of this grant, we are planning the setup for our National Particle Therapy and Research Center (NPTRC). We are working on the organizational structure, major research directions and the details of the research framework needed to conduct the proposed research topics. The organizational chart of the NPTRC can be seen in Figure 1.

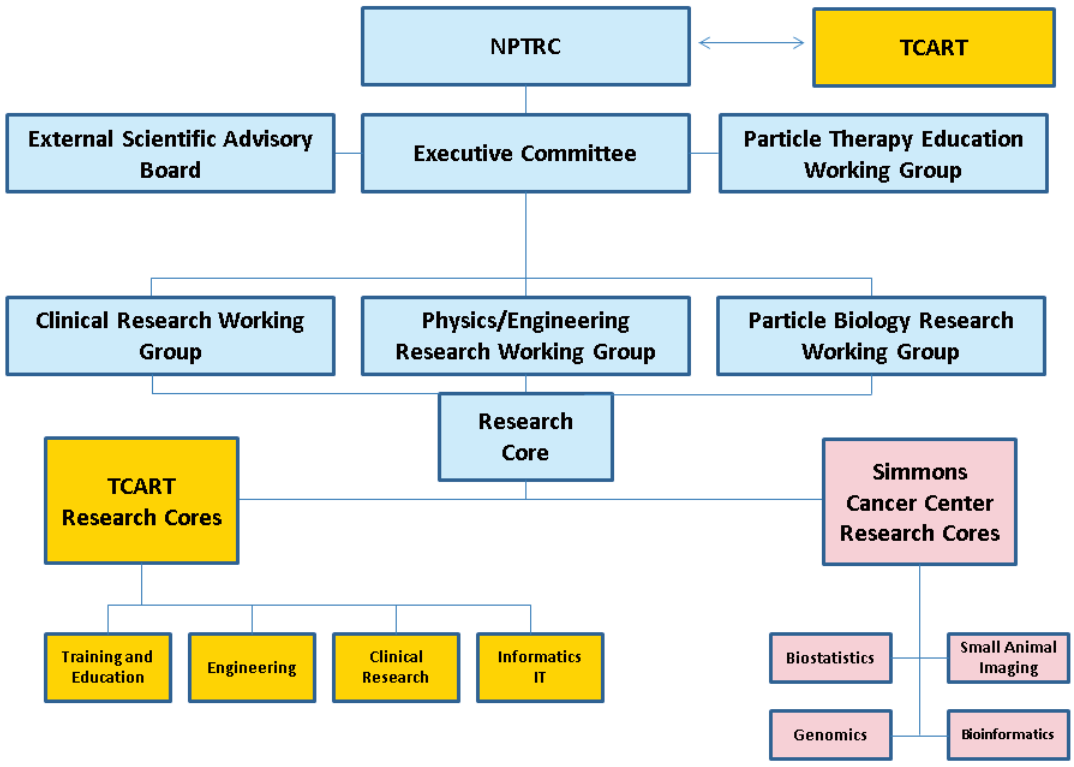

Figure 1: UT Southwestern's planned National Particle Therapy and Research Center (NPTRC). The organizational chart of the NPTRC is composed of an executive committee, an external advisory board and research working groups (biology, physics and clinical).

UT Southwestern's success to secure federal funding to plan the research component of the heavy ion therapy system was noticed by the State of Texas legislators. UTSW applied and successfully secured a 2:1 matching fund from the State of Texas. This grant is also spanning 2015 to 2017. The grant enables UTSW to plan the therapeutic component of our initiative as well as planning the system as a whole. First, we established a consortium of major academic Texas institutions interested in working with UTSW in the field of heavy ion therapy and research. The researchers from these institutions have a strong desire to conduct research at our envisioned heavy ion facility and using its services for patient care. We have already established the framework and organizational structure of the Texas Center for Advanced Radiation Therapy (TCART). This is an umbrella center that unites our conventional X-ray therapy center with the planned heavy ion therapy center. The organizational chart of the TCART is reported in Figure 2.

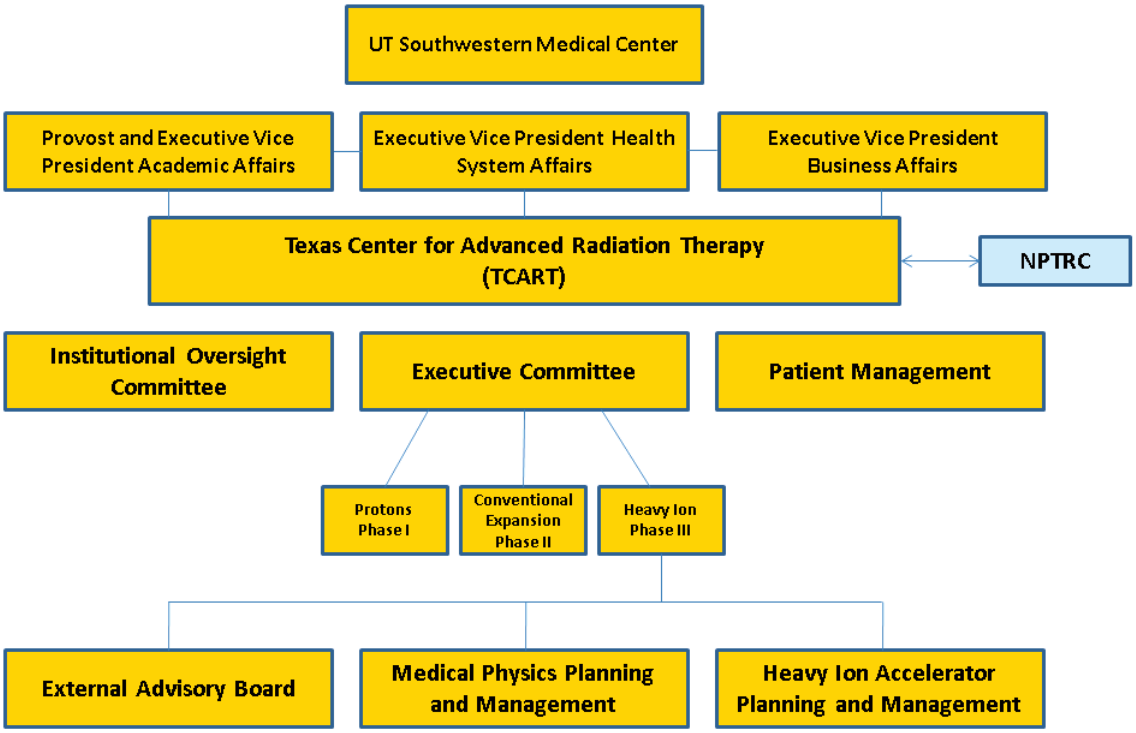

Figure 2: The Texas Center for Advanced Radiation Therapy (TCART) will unite our conventional photon therapy systems and a heavy ion therapy facility.

We have hired three external independent consultant groups to support the planning of both the NPTRC and TCART. Their findings and recommendations will supplement our internal planning results. The goal of these three groups was to: i) evaluate heavy ion accelerating and delivery technology currently available on the market; ii) offer independent view on how to construct business models for heavy ion irradiation; iii) independently estimate the construction cost of the heavy ion part of our proposed TCART.

Conclusions

The UT Southwestern Medical Center in Dallas is strategically located to build the first hospital based heavy ion therapy and research center in the United States. We were able to secure federal funding provided by NCI to plan the research component of the heavy ion therapy machine. In addition to this federal funding, we secured State of Texas funding to plan the therapeutic part of the heavy ion system. Independent consultant companies were hired to advise us about heavy ion technology, about business plan construction and estimation of the building cost. The selection of the technology will be made in the near future. We envision the first patient to be treated at our facility in 2021.

The UCSF / North American Particle Therapy Alliance Plans for a National and International Program in Ion Beam Therapy Research - 2016 Update

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Abstract

The North American Particle Alliance was founded to support efforts for establishing a National Center for Particle Beam Radiation Therapy (PBRT) Research in the United States with international participation. The research center will be associated with an independently funded clinical facility for PBRT. In February 2015, NAPTA was awarded one of two P20 research grants from the National Cancer Institute. Here we report on the activities that took place during the first year of P20 funding and progress made with respect to the various challenges of developing sustainable, clinically centered PBRT research.

Introduction

Ion beam therapy originated at the Lawrence Berkeley National Laboratory (LBNL) in California with pioneering work by C.A. Tobias et al at the 184-Inch Synchrocyclotron with clinical applications of proton and helium beams, with over 1000 patients treated through 1974 with high-energy plateau radiation for mostly pituitary fields [1]. In 1975, LBNL and the University of California, San Francisco (UCSF) continued this development by conducting a series of radiobiological [2] and clinical studies [3] with different ion species including helium and neon beams. These studies involved more than 2,000 patients with solid tumors and arteriovenous malformations. The LBNL-UCSF program ended in 1993 with the budget-forced closure of the LBNL treatment facility. From this initial experience much insight into ion radiobiology and clinical experience was gained. In particular, we learned that there was much promise in the physical and radiobiological characteristics of ions that makes them attractive for tumors difficult to cure with photon or proton therapy but that further technological development and basic research was needed and that only randomized trials would eventually answer the key questions surrounding the value of ions in radiation therapy. The clinical experience with carbon ions for radiation therapy continued at the National Institute of Radiological Sciences (NIRS) in Japan and at the Gesellschaft für Schwerionenforschung (GSI) in Germany. To date more than 10,000 patients have been treated with carbon ions in Japan, Europe, and China and this number is slowly increasing as more carbon facilities have opened or are under development. However, no randomized trials with carbon ions have been completed to date and experience with other ions heavier than protons has not further been gained.

Recognizing the need for more research in ion beam therapy, the U.S. National Cancer Institute (NCI) and Department of Energy (DOE) jointly organized a workshop on ion beam therapy in Bethesda, MD, January 2013, where more than 60 experts convened to define needs and challenges in ion beam therapy (including

protontherapy[1]. In order to further advance research of the potential benefits and clinical usefulness of particle beam therapy approaches to cancer treatment. NCI and DOE subsequently released separate but related requests for research proposals: (1) proposals for planning efforts establishing a National Center for Particle Beam Radiation Therapy (PBRT) Research in conjunction with an independent commitment to construct a clinical facility in the U.S. (NCI P20 grants), and (2) applications supporting new efforts to develop the next generation of particle accelerators and magnets guiding ion beams, in order to make these key technology components smaller, lighter, and much less costly (DOE Accelerator Stewardship Program). In response to the former announcement, the *North American Particle Therapy Alliance* (NAPTA) was formed in February 2013 and was awarded one of the two P20 grants the NCI, the second going to the University of Texas (UT) Southwestern Dallas.

NAPTA brings together U.S. experts in radiation oncology, medical and accelerator physics, magnet design, and radiobiology with international experts from the ion beam facilities in Germany, Italy, China, and Japan. NAPTA's initial primary focus, currently funded by the P20 grant, is to build the infrastructure needed to facilitate research in optimizing PBRT delivery and clinical trial design. The long-term goal of NAPTA is to perform clinically relevant research using protons and other light ions up to neon in the future PBRT clinical center. The purpose of this contribution is to summarize what has been accomplished in the first year of NAPTA's P20 grant and to give an outlook and what is next.

The seven major challenges of particle beam therapy

In its initial review the NAPTA P20 team at UCSF identified 7 major challenges that need to be overcome in order to advance PBRT to its next stage, which were cast into the acronym "RESIDUE" [4]. These challenges include, without any relevance to the order of listing, the following:

1. Radiobiology to address uncertainty in optimal fraction sizes and doses and RBE (biological)
2. Exchange of technology, funding, and infrastructure between academic centers, payers, industry and funding agencies (operational)
3. Size/weight of accelerators and gantries (accelerator physics/engineering)
4. Integration of technology to advance key areas from beam acceleration and delivery, through treatment planning and image guidance (medical physics/engineering/computer science)
5. Define the patient population to be studied; that is, "who really needs PBRT" (clinical)
6. Uncertainties of dose and range at the end of the Bragg peak (imaging and detector physics)
7. Evidence of clinical effectiveness and cost-effectiveness (societal)

[1] http://science.energy.gov/~/media/hep/pdf/acceleratorrdstewardship/Workshop_on_Ion_Beam_Therapy_Report_Final_R1.pdf

Progress made towards meeting these challenges

During the first 10 months of our P20 grant we have begun activities addressing these RESIDUE challenges as outlined in the following subsections.

Radiobiology

A radiobiology meeting, addressing RESIDUE challenge 1, was held by teleconference on September 15, 2015. Participation, which was by invitation, included 10 radiation biologists and other interested scientists from UCSF, MGH, Stanford, UCLA, and UTSW. The meeting addressed one of the key questions in particle therapy radiobiology: Whether heavy charged particles would result in a more robust immune response than x-ray or proton based radiation. The meeting participants shared their knowledge on what is known about molecular mechanisms or radiation that could stimulate the immune response, what is the dose fraction size dependence of that response, and whether we can design clinical trials that compare the immune response to proton and ion therapy to stereotactic body radiation therapy with photons for specific tumors sites, including lymphoma, melanoma, and renal carcinomas in particular, and possibly other radioresistant tumors.

The traditional line of investigating the benefits of ion beam therapy has been to treat cancer focusing on the local treatment of relatively radiation-resistant and in many cases relatively rare cancers [5]. However, there is limited preclinical and anecdotal clinical evidence that, in addition to local effects, ion beam therapy appears to reduce the metastatic potential of tumors. For example, Ogata et al. examined the biological properties of highly aggressive HT1080 human fibrosarcoma cells to assess their metastatic processes in terms of cell adhesion capability to extracellular matrix, expression of integrins, cell migration, cell invasive capability, and matrix metalloproteinase-2 activity *in vitro* [6]. They showed that carbon ion irradiation suppressed metastatic potential even at lower dose, whereas photon irradiation promoted cell migration and invasive capabilities at lower dose level, and thus provided preclinical evidence that ion beam radiotherapy may be superior to conventional photon beam therapy in possible preventive effects on metastases of irradiated malignant tumor cells. A number of recent studies have shown that radiation can play a critical role in the tumor-related immune response [7]. The body of work suggests that radiation therapy generates an *in situ* vaccine by inducing release of antigens in association with pro-inflammatory signals that trigger the innate immune system to activate tumor-specific T cells overcoming some of the barriers to tumor rejection. For 2016, we are planning to launch a collaborative research program addressing this compelling question. Our proposal will systematically investigate whether there is differential benefit to the use of carbon ions to induce such responses. The proposed work will involve several lines of investigation to determine whether surrogates or markers for this differential effect can be identified and utilized clinically. If successful, we will be able to show that in addition to use against relatively rare locally advanced tumors, there may be a role for ion beam therapy in treating patients with advanced local and/or systemic disease in conjunction with immunologic therapeutic agents.

Accelerator physics and engineering

A meeting on this topic, addressing RESIDUE challenge was held by teleconference on September 29, 2015 to discuss particle therapy accelerators and beam delivery systems. Participants included 8 accelerator, magnet, and gantry experts participating from BNL, LBNL, PAC/NFAL and SLAC along with the 4 P20/NAPTA team leaders and Pilot Projects co-PI's and a radiation oncologist with long-standing interest in particle therapy (Dr. James Welsh from Loyola University). The meeting was called to address a key technology challenge: To define the technology that we should develop to achieve the necessary level of compactness and cost-effectiveness for ion beam delivery systems in the next 5 years. In other words, what is the most promising compact medical accelerator and beam line design that would serve our needs for proton and ion therapy? A summary of the major conclusions from this meeting follows:

1. Ion gantries are desirable, but the real need for 360 degree gantries remains an open question that should be studied scientifically. Other options to direct the beam to the tumor from different angles exist and are being explored or designed.
2. Superconducting magnets would make gantries much more compact, but one needs to pay attention to momentum acceptance and speed of scanning in the longitudinal (beam) direction.
3. Fixed field alternating gradient (FFAG) accelerators are an attractive design concept for the next generation of medical ion accelerators. A scoping study that puts medical needs upfront is desirable.
4. The only other reasonable option seems to be the rapid cycling synchrotron (RCS) developed at BNL, but FFAG would clearly have advantages in terms of compactness and speed.
5. Nonetheless, classical cyclotrons and (slow-repetition) synchrotrons should not be considered an option.
6. Starting with helium ions is attractive as it would ease the development. Later upgrade to heavier ions and adding additional rooms to a single vault seems feasible.
7. One should pay attention to integrating particle (proton or helium) imaging in future beam lines.
8. Separation of low-intensity imaging and high-intensity treatment is important for future designs.

Many of the points mentioned were also discussed at the NAPTA review meeting at ASTRO in October 2015, and at the workshop entitled "Ion Beam Therapy: Clinical, Scientific and Technical Challenges" at the Queen Elizabeth University Hospital, Birmingham, UK, January 19-20, 2016, see http://indico.cern.ch/event/456299/.

P20 pilot research

The NAPTA team at UCSF is engaged in pilot research addressing the range uncertainty of ion beams (RESIDUE challenge 4) and the uncertainty of RBE of ion beams (RESIDUE challenge 1). The UCSF investigators leverage their collaboration with the proton CT (pCT) collaboration that has successfully built a pre-clinical proton CT scanner with funding from the National Institute of Biomedical Imaging and Bioengineering. The pCT scanner has been shipped to the Northwestern Medicine Chicago Proton Center (CPC) in Warrenville, IL, where it has been used for ongoing studies of proton CT. One should remember that the concept of NAPTA is to develop research capabilities as a virtual center, utilizing existing expertise in different parts of the world and organizing it in a synergistic fashion before the National Center for Particle Beam Radiation Therapy Research comes into existence.

The RBE problem will be addressed by utilizing an entirely new approach based on clustering of ionizations on the nanometer level. The underlying assumption is that the biological effect for a given biological system is mostly determined by the frequency of intermediate to large clusters of ionization in volumes of DNA dimensions. Thus equal biological effectiveness would be achieved by obtaining a uniform cluster size distribution throughout the target volume. Clustering statistics can, in principle, be obtained from Monte Carlo simulations, that would need to be validated with experimental nanodosimeters. This is a very active field of research that will be part of the NIH funded P20 pilot research in 2016.

Planning for enhancement of clinical PBRT research

A major research question of NAPTA and the P20 project (RESIDUE challenges 5 and 7) has been to define the best strategy to determine whether the trials testing ions heavier than protons should involve primarily the treatment of radiation-resistant tumors as traditionally discussed in the literature [5], or whether the issue of a differential response to the immune response, should be a key first step. This was already mentioned under Radiobiology above and was further discussed at the ASTRO NAPTA meeting in October 2015. From the discussion with our NAPTA colleagues we have determined that because it will take at least 5 years (or more) for a clinical ion treatment facility to be built in the USA, and there is currently no reimbursement for the use of

this technology, definitive evidence based on randomized trials conducted in the USA are not likely to be launched and completed in the next few years. If we could demonstrate that there is a differential benefit to the use of ions to induce enhanced immune responses, the time to complete trials could be shortened. We further determined that it would be feasible to launch the desired Phase I-II trials using the existing ion beam facilities available via our NAPTA collaborators in Japan, China, Germany and Italy, now if we could acquire funding to support treatment there. At this point, we have engaged representatives from the NCI, FDA, and CMS to discuss funding issues related to the trials we would like to launch. Although the FDA and NCI are generally supportive of our plans, the representatives from CMS informed us that it currently not possible for them to provide financial support for clinical treatment in a foreign country, except for emergencies. In 2016, we will engage contacts at the NCI and Congress to change this ruling and move our plan to utilize existing ion beam facilities forward.

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Appendix

Summary of typical clinical results at HIMAC

(Period: June 1994 – February 2013)

Protocol	ID No	Phase	Applicability, radiation method (fraction numbers / week or day)	Number of patients	3-year local control ratio	Survival ratio		Remarks
						3 years	5 years	
Head and neck	(9301)	I/II	18 times / 6 weeks	34	81%	48%	37%	
Head and neck II	(9504)	I/II	16 times / 4 weeks					
○ Head and neck III	(9602)	II	16 times / 4 weeks	455	83%	69%	55%	AM since 2003
○ Head and neck IV (bone and soft tissue)	(0006)	I/II	16 times / 4 weeks	44	89%	71%	52%	AM since 2008
○ Head and neck V (malignant melanoma)	(0007)	II	16 times / 4 weeks, CB with chemotherapy	120	82%	62%	50%	AM since 2003
Non-small-cell lung	(9303)	I/II	Lung field type + pulmonary hilum proximity type + local advanced cancer, 18 times / 6 weeks	47	65%	64%	41%	
Non-small-cell lung II	(9701)	I/II	Lung field type, 9 times / 3 weeks	34	91%	55%	40%	
○ Non-small-cell lung III	(9801)	I/II	Pulmonary hilum proximity type, 9 times / 3 weeks	23	91%	64%	31%	AM since 2003
Non-small-cell lung IV	(9802)	II	Pulmonary peripheral type, 9 times / 3 weeks	50	95%	66%	50%	
○ Non-small-cell lung V	(9903)	I/II	Local advanced type, 16 times / 4 weeks	37	93%	38%	32%	AM since 2003
Non-small-cell lung VI	(0001)	I/II	Pulmonary peripheral type, 4 times / 1 week	79	90%	62%	36%	
○ Non-small-cell lung VII	(0005)	I/II	Pulmonary hilum and mediastinal lymph node metastasis, 12 times / 3 weeks	21	94%	36%	6%	AM since 2012
○ Non-small-cell lung VIII	(0201)	I/II	Lung field type, 1 time / 1 day	151	83%	76%	55%	AM since 2012
Non-small-cell lung IX	(0503)	I/II	Pulmonary hilum and hilum proximity type, 12 times / 3 weeks	18	100%	60%	34%	
Hepatoma	(9401)	I/II	15 times / 5 weeks	24	81%	50%	25%	
Hepatoma II	(9603)	I/II	12 times / 3 weeks → 8 times / 2 weeks → 4 times / 1 week	82	87%	48%	26%	
Hepatoma III	(0004)	II	4 times / 1 week	44	96%	58%	35%	
○ Hepatoma IV	(0202)	I/II	2 times / 2 days	144	79%	62%	34%	AM since 2006
Metastatic liver	(0506)	I/II	1 time / 1 day	25	38%	86%	64%	
Prostate	(9402)	I/II	CB with hormones	35	97%	94%	89%	
Prostate II	(9703)	I/II	Carbon alone and CB with hormones	61	100%	97%	90%	
○ Prostate III	(9904)	II	20 times / 5 weeks → 16 times / 4 weeks → 12 times / 3 weeks	1247	99%	98%	96%	AM since 2003
○ Prostate V	(1002)	I/II	12 times / 3 weeks	68	100%	96%	-	AM since 2013
Kidney	(1203)	I/II	12 times / 3 weeks	1	-	-	-	Just begun

Remarks and Terms

ID No. : (93xx) means this protocol has been adopted in 1993.

Phase : [Phase I study]
A study that involves stepwise increases in radiation dose for the purpose of ensuring safety. For radiation therapy, a study at dose too low to treat cancer are not carried out, so a phase I study and a phase II study are often considered a single step when a study is carried out.
[Phase II study]
A study that involves treatment by methods determined separately for each patient group under identical conditions, checking effectiveness and safety in order to determine the final method to utilize.

AM : Advanced medical technology
○ It is the intermediate stage between the research and the National Health Insurance. It is provided by Special Functioning Hospitals approved by Japanese Ministry of Health, Labor, and Welfare.

CB : Combination with other treatment method

Protocol	ID. No	Phase	Applicability, radiation method (fractionated irradiation doses / week or day)	Number of patients	3-year local control ratio	Survival ratio		Remarks
						3 years	5 years	
Cervical	(9403)	I/II	Evenly dose	30	49%	40%	37%	
Cervical II	(9702)	I/II	Dose escalation for primary area only	36	72%	52%	45%	
○ Cervical III	(9902)	I/II	20 times / 5 weeks					AM since 2014
○ Uterus IV	(0508)	I/II	20 times / 5 weeks	26	75%	58%	54%	AM since 2012
Uterus V	(1207)	I	20 times / 5 weeks, CB with chemotherapy	4	-	-	-	Just begun
Uterus VI	(1302)	I/II	20 times / 5 weeks, CB with chemotherapy	0	-	-	-	Just begun
○ Uterus adenocarcinoma	(9704)	I/II	12 times / 3 weeks + 8 times / 2 weeks boost	67	59%	53%	38%	AM since 2012
○ Uterus adenocarcinoma II	(1001)	I/II	12 times / 3 weeks + 8 times / 2 weeks boost	19	-	-	-	AM since 2014
Breast I	(1301)	I/II	4 times / 1 week	3	-	-	-	Just begun
Bone and soft tissue	(9501)	I/II	16 times / 4 weeks	57	63%	47%	36%	
○ Bone and soft tissue II	(9901)	Ⅱ	16 times / 4 weeks	589	79%	69%	58%	AM since 2003
Esophagus (pre-surgery)	(9502)	I/II	20 times / 5 weeks	7	-	*14%	-	*2-year survival
Esophagus (radical)	(9503)	I/II	24 times / 6 weeks	14	-	*7%	-	*2-year survival
Esophagus (post-surgery)	(9905)	I/II	Nonresectable, 12 times / 3 weeks	2	-	-	-	
Esophagus (shortly pre-surgery)	(0301)	I/II	8 times / 2 weeks	31	-	74%	59%	
Esophagus (pre-surgery)	(1206)	I/II	8 times / 2 weeks, CB with chemotherapy	0	-	-	-	Just begun
Period-I esophagus (radical)	(0701)	I/II	12 times / 3 weeks	16	75%	100%	86%	
○ Rectum postoperative	(0003)	I/II	16 times / 4 weeks	197	89%	67%	42%	AM since 2004
○ Skull base	(9601)	I/II	16 times / 4 weeks	84	93%	92%	85%	AM since 2004
Pancreas I (pre-surgery)	(9906)	I/II	16 times / 4 weeks	22	*86%	*20%	-	*2-year control/survival
○ Pancreas II (pre-surgery)	(0203)	I/II	8 times / 2 weeks	35	86%	40%	40%	AM since 2011
Pancreas V (pre-surgery)	(1205)	I	8 times / 2 weeks, CB with chemotherapy	3	-	-	-	Just begun
Pancreas III	(0204)	I/II	Local advanced, 12 times / 3 weeks	47	*70%	*11%	-	*2-year control/survival
○ Pancreas IV (CB with chemotherapy)	(0513)	I/II	Local advanced, 12 times / 3 weeks	81	*33%	*47%	-	AM since 2012
Eye	(0002)	I/II	5 times / 8 days	127	96%	89%	80%	AM since 2004
Lacrimal gland	(0102)	I/II	12 times / 3 weeks	21	76%	69%	69%	AM since 2011

Specifications

Name of institute or hospital	National Institute of Radiological Sciences	Hyogo Ion Beam Medical Center	Institute of Modern Physics (IMP), Chinese Academy of Sciences
Name of facility	Heavy Ion Medical Accelerator in Chiba	Hyogo Ion Beam Medical Center	Heavy Ion Research Facility in Lanzhou
Abbreviation of facility	HIMAC	HIBMC	HIRFL
Location City (Country)	Chiba (Japan)	Hyogo (Japan)	Lanzhou (China)
Start year (mm/yy)	June 1994	April 2001	11/2006
Type of accelerators	Synchrotron + RFQ linac & DT linac	Synchrotron + RFQ linac & DT linac	Cyclotron + Synchrotron
Number of ion sources	4	2	1
Typical operation schedule (hour/day/month)	24 hours / 6 days / 10 months	16 hours / 5 days / 12 months	24 hours / 7 days / 11 months
Maintenance schedule (length / interval)	1 month / a half year	43 days / a year	1 month / a year
– Treatment ability			
Irradiation method	Wobbler (4 ports), Pencil beam scanning (4 ports)	Wobbler (5 ports), Pencil beam scanning (0 ports)	Uniform scanning (1 port), Pencil beam scanning (1 port)
Ion species	Carbon	Carbon, Proton	Carbon
Maximum beam energy (MeV/u)	430 (Carbon)	375 (Carbon), 230(Proton)	1000 (Carbon)
Maximum beam intensity (particle per second)	1.8E9 (Carbon)	3.6E9 (Carbon), 8.2E10(Proton)	5E8 (Carbon)
Typical dose rate at patient (GyE/min.)	5 (Carbon)	3.5 (Carbon, SOBP60mm, 16cm ϕ), 4.0 (Proton, SOBP60mm, 16cm ϕ)	2 (Carbon)
Number of treatment rooms	5	5	2
Number of treatment rooms (under construction)	1	0	0
Number of irradiation ports (Horizontal)	4	2	1
Number of irradiation ports (Vertical)	4	1	1
Number of irradiation ports (Others)	1 (rotating gantry under construction)	2 (rotating gantry)	
Typical treatment schedule (hour/day/week)	10 hours / 4 or 5 days / week	8 hours / 5 days / week	8 hours / 7 days / week
Typical patient number (Number / day)	60 – 100	60 – 100	10–15
Typical patient number (Number / year)	900	700	60
Total number of patients (till mm/yy)	9340 (August 2015)	7258 (November 2015)	213 (December, 2015)
Major diseases	Prostate, Bone & Soft tissue, Head & Neck, Lung, Liver, Pancreas, Rectum	Hepatobiliary, Pancreas, Bone & Soft tissue, Head & Neck, Lung, Prostate	Bone&Soft tissue, Head&Neck, Lung, Liver
– Research ability			
Available ion species	from H to Xe	H, C, He	from p to U
Number of experiment rooms	4	1	12
Number of experiment rooms (under construction)	0	0	0
Typical experiment schedule (hour/day/week)	10 hours / 6 days / week	any time	24 hours / 7 days / week
Major purpose of experiments	Biology, Physics	Biology, Physics	Radiobiology, Nuclear Physics, Material science, Space science

Please add asterisk (*) to planned value for facilities under construction

Heidelberg University Hospital	Gunma University	Italian National Center for Oncologic Hadrontherapy	Ion Beam Therapy Center, SAGA HIMAT Foundation
Heidelberg Ion-Beam Therapy Center	Gunma University Heavy Ion Medical Center	Italian National Center for Oncologic Hadrontherapy	SAGA HIMAT (Saga Heavy Ion Accelerator in Tosu)
HIT	GHMC	CNAO	SAGA HIMAT
Heidelberg (Germany)	Maebashi(Japan)	Pavia (Italy)	Tosu (Japan)
November 2009	March 2010	September 2011	August 27, 2013
Synchrotron + RFQ linac & DT linac	Synchrotron + Linac (RFQ & IH-DTL)	Synchrotron	Synchrotron + RFQ linac & DT linac
4	1	2	1
24 hours / 7 days / 11 months	17 hours / 6 days / 11 months	24 hours / 7 days / 12 months	15 hours / 5 days / 12 months
1-2 weeks / six months	1 month / a year	5 days/ quarterly	2 weeks / one year
intensity-controlled raster scanning	Broad Beam (Scatterer + Wobbler)	Pencil beam scanning (4 ports)	Wobbler (4 ports), *Pencil beam scanning (2 ports)
Proton, Helium, Carbon, Oxygen	Carbon	Carbon, protons	Carbon
220 (Proton), 330 (Helium), 430 (Carbon), 430 (Oxygen)	400 (Carbon)	398,84 (Carbon) 228,57 (protons)	400 (Carbon)
	1E9 (Carbon)	7E8 (Protons), 4E7 (Carbon)	1.0E9 (Carbon)
	5 (Carbon)	2	5 (Carbon)
3	3	3	2
0	0 (1room is planned to be used as a treatment room with a method of scanning)	0	*'1
2	2	3	3 (*1)
0	2	1	2 (*1)
1 (rotating gantry)	1 vertical port is planned to be used for treatment with a method of scanning.	0	1 (45 degree oblique)
10 -12 hours / 6 days / week	8 hours / 4 or 5 days / week	12 hours / 4 or 5 days / week	8 hours / 4 days / week
50-70	35 - 60	30 - 35	40
650	400	400 - 500 (2016)	600
3192 (November 2011)	1887 (November 2015)	690 (September 2011)	1054 (November 13, 2015)
CNS, skull base, head and neck, pelvis, pediatric tumours	Prostate, Lung, Liver, H&N, B&S, Pancreas	Bone & Soft tissues sarcomas, Head & Neck tumours, recurrent tumours	Prostate, Bone & Soft tissue, Head & Neck, Lung, Liver, Pancreas, Recurrent rectal
H, He, C, O	Carbon	H, C	Carbon
1	1	0	0
0	0	1 (planned 2017)	0
12 hours / 6 days / week	4 hours / 1 day / week, '10 hours/ 2 days / weekend	8 hours / 1 day / week	0 hours / 0 days / week
Biology, Physics	Biology, Physics	Biology, Physics	

Name of institute or hospital	Shanghai Proton and Heavy Ion Center, Proton and Heavy Ion Center, FUSCC		Kanagawa Cancer Center
Name of facility	Shanghai Proton and Heavy Ion Center	Marburg Ion-Beam Therapy Center	Ion-beam Radiation Oncology Center in Kanagawa
Abbreviation of facility	SPHIC	MIT	i-ROCK
Location City (Country)	Shanghai (China)	Marburg (Germany)	Yokohama (Japan)
Start year (mm/yy)	May 2015	Oct-15	* December 2015
Type of accelerators	Synchrotron + RFQ linac & IH linac		Synchrotron + RFQ linac + IH linac
Number of ion sources	2		1
Typical operation schedule (hour/day/month)	12 hours / 5 days / 12 months		* 12hours / 4 days / 11 months
Maintenance schedule (length / interval)	4days / (1/4 year)		* 1 month / year
- Treatment ability			
Irradiation method	Raster scanning beam (4 ports)	Raster scanning	Pencil beam scanning (6 ports)
Ion species	Carbon & Proton	Proton, Carbon	Carbon
Maximum beam energy (MeV/u)	430 (Carbon)/250(Proton)	430 (Carbon)	430
Maximum beam intensity (particle per second)	1.0E9 (Carbon)/2.0E10(Proton)	2E10 pps (Proton), 3E8 pps (Carbon)	1.2E9 (Carbon)
Typical dose rate at patient (GyE/min.)	/		2 (Carbon)
Number of treatment rooms	4	4	4
Number of treatment rooms (under construction)	0		
Number of irradiation ports (Horizontal)	3	3	4
Number of irradiation ports (Vertical)	0		2
Number of irradiation ports (Others)	1 (Oblique 45°)	1 (45 degree)	0
Typical treatment schedule (hour/day/week)	8 hours / 5 days / week		* 8 hours / 4 days / week
Typical patient number (Number / day)	20-40		* at 20 pts/day at first year, and about 80 pts/day in full.
Typical patient number (Number / year)	500		* 200 pts/y at first year, and 880 pts/y in full.
Total number of patients (till mm/yy)	117 (November 2015)		
Major diseases	Head & Neck, Prostate, Bone & Soft tissue, Lung,		* Lung, Liver and pancreas, Head & neck, Prostate, Bone & Soft tissue
- Research ability			
Available ion species	H, C		Carbon
Number of experiment rooms	0		0
Number of experiment rooms (under construction)	0		0
Typical experiment schedule (hour/day/week)	0		
Major purpose of experiments	Biology, Physics		
		(Information in 2010)	

Please add asterisk (*) to planned value for facilities under construction

EBG MedAustron GmbH	Gansu Wuwei Tumor Hospital	Osaka cancer therapy incorporated foundation (tentative name)	Korea Institute of Radiological & Medical Sciences	Yamagata University Hospital
MedAustron	Heavy Ion Therapy Facility in Wuwei	Osaka carbon ion therapy caner center (tentative name)	Korea Heavy Ion Medical Accelerator Project	TBD
MedAustron	HITFiW	OCC (tentative name)	KHIMA	TBD
Wiener Neustadt (Austria)	Wuwei (China)	Osaka (Japan)	Busan (Republic of Korea)	Yamagata (Japan)
2016		April 2018	09/2018 (*)	October 2019*
Synchrotron		Synchrotron + RFQ linac & APF-IH linac	Synchrotron + RFQ linac & DT linac (*)	Synchrotron + RFQ linac & DT linac
4		1	2 (*)	1
		11 hours/ 6 days/ 12 months		TBD
		(Total 16-20 days) 4-5 days / a quarter of the year		TBD
Pencil beam scanning		Pencil beam scanning	Wobbler (2 ports), Pencil beam scanning (3 ports) (*)	Pencil beam scanning (3 ports)*
Protons, Carbon Ions		Carbon	Carbon/Proton (*)	Carbon
250 (protons), 400 (Carbon Ions); 800 (protons, experimental room)		430	430 (Carbon) / 230 (Proton) (*)	430 (Carbon)*
1E10 (protons) 1E8 (Carbon ions)		2.0E9	1.33E8 (Carbon)/3.33E9 (Proton) at isocenter (*)	1E9 (Carbon)*
		5	5 (Carbon)/2.2 (Proton) (*)	5 (Carbon)*
3		3		
		None	3 (*)	2*
2		3	3 (2 for scanning, 1 for wobbler) (*)	1*
1		1 ports, and add 1 port in the future	2 (1 for scanning, 1 for wobbler) (*)	1*
1 (rotating gantry for protons under construction)		1 (45-degree)	1 (Research room) (*)	1 (rotating gantry)*
		7 hours/ 5 days/ week		TBD
		60-90		
		1200 (a future prospect or potential)		
		4,280 patients till march 2023		
		Prostate/Lung/Liver/Head & Neck		
Proton, carbon ions		Carbon	Carbon/Proton (*)	Carbon
1		0		
1		0	1(*)	TBD
		None		TBD
Biology, Physics		None	Biology, Physics (*)	TBD

2nd International Symposium on Heavy-Ion Radiotherapy and Advanced Technology

- Date of Publishing: January 2016

- International Affairs Section
  Dept. of Planning and Management
  National Institute of Radiological Sciences
  Anagawa 4-9-1, Inage-ku, Chiba, 263-8555, Japan
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  http://www.nirs.go.jp/ENG/index.html

NIRS-M-283 Printed in Japan

National Institute of Radiological Sciences
2nd International Symposium 2016
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