Twenty Years of Carbon Ion Radiation Therapy at the National Institute of Radiological Sciences: Accomplishments and Prospects

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Introduction

In response to Japan’s first comprehensive 10-year strategy for cancer control and the aim to use carbon ion beams to irradiate cancer cells, the world’s first heavy ion accelerator designed for medical use, the Heavy Ion Medical Accelerator in Chiba (HIMAC), was opened at the National Institute of Radiological Sciences (NIRS), Chiba, Japan, in 1994, and clinical trials on carbon ion radiation therapy (CIRT) began. From that time, and with the cooperation of experts throughout Japan, a clinical research network has been constructed, and in the past 20 years more than 9000 cancer patients have been treated with CIRT. In so doing, we have found particular success in the treatment of difficult-to-cure, intractable cancers for which other treatment options fall short, and our results using this cutting-edge method of radiation therapy have attracted attention throughout the world [1]. Based on the results of these clinical studies, in 2003 the Japanese government recognized CIRT as an “advanced medical technology” for the treatment of solid tumors, and from that year we have been able to offer treatment to patients for a variety of malignancies. In 2004, we succeeded in reducing the size and cost of our CIRT equipment to one third that of the original, and the prototype was placed at Gunma University with operation beginning in 2010. That machine’s successor was developed at NIRS and then placed in Saga Prefecture’s Tosu City, beginning operation there in 2013. Research into treatment methodology has progressed as well: in 2011, a next-generation irradiation technique known as the scanning irradiation method was incorporated into the HIMAC at NIRS, and already more than 700 patients have received therapy by this method. Currently, a new system capable of the scanning irradiation method is being built in Kanagawa Prefecture that is planned to open by the end of 2015. Though the scanning method presents a difficulty when used in the treatment of respiration-mobile tumors/organs, at NIRS we have successfully developed a fast multiple scanning (“rescanning”) system that is capable of delivering treatment simultaneous with natural patient respiration, and clinical trials began in March 2015. In comparison with the passive beam method predominantly used at the HIMAC up until 2011, the scanning method offers further potential for miniaturizing the beam scattering and irradiation-field–forming equipment, and research is ongoing into this potential. Simultaneously, we have developed a small, lightweight, rotating gantry platform equipped with superconductive magnets, which is under construction and has a target date of early 2016 (Figure 1).

In this article, we will review the experience and results at NIRS up until now, examine the future outlook of CIRT, and introduce our plans for future developments.
and a highly conformal, high dose peak to the terminal edge of a target. To effectively utilize these beam characteristics, at NIRS research was begun into shortening treatment time and treating diseases that are highly radiation resistant and conventionally difficult to treat.

Use of CIRT began in June 1994; at first it consisted of phase I/II clinical trials (dose escalation studies to confirm safety and efficacy), then later switched over to phase II clinical trials to examine tumor-type-specific outcomes. Patient numbers increased from November 2003, when CIRT treatment for general patients was authorized, and as of March 2015, 9021 patients have been registered at the institute. The demographics of these patients can be seen in Figure 2. The majority were treated for prostate cancer, followed by bone and soft tissue sarcomas; head and neck, lung, liver, and pancreatic tumors; and retreatment of postsurgical locally recurrent rectal cancer, among others.

In the phase I/II clinical trials, in order to delineate the safety and confirm the efficacy of CIRT, for each disease the number of fractions and duration of treatment was fixed, and the irradiation dose was increased by 5% to 10% stepwise over the

Figure 1. Carbon ion lightweight rotating gantry platform equipped with superconductive magnets.

Figure 2. Demographics of the patients treated with carbon ion radiation therapy at the National Institute of Radiological Sciences from June 1994 to March 2015.
course of the study. The recommended dose of the phase I/II trial was carried over into phase II clinical trials. Furthermore, for each disease, phase I/II clinical trials were conducted to investigate shortening the irradiation time frame by dose hypofractionation.

As shown in Figure 3, generally the number of trial-registered patients has increased each year. This is due to the smooth establishment of irradiation methodologies via clinical trials and has been further enhanced by the drastic shortening of the treatment time frame via hypofractionation. In 2013, the number of treatments delivered reached nearly 1000 patients. Currently, the average number of fractions per person is less than 12, with an average treatment time frame of 3 weeks. This initiative to shorten the length of treatment time and reduce fractionation number greatly enhanced the efficient use and ongoing development of the CIRT equipment.

Beginning in June 1994, all CIRT cases were treated as clinical trials. In November 2003, the Japanese government designated solid tumor targeting carbon ion radiotherapy as an “advanced medical technology,” and CIRT was opened to the general population for treatment outside the national health insurance system. Though CIRT is now part of the general therapeutic landscape of Japan, improvements in disease-specific treatment methods and treatment adaptation expansion are necessary, so clinical trials continue, and about 20% of patients are enrolled in clinical trials.

Treatment Results
In reviewing all of this clinical experience, we can see that CIRT is especially effective for the certain conditions. In terms of disease type, CIRT is effective for head and neck (including eyes), skull base, lung, liver, pancreas, and prostate tumors; bone and soft tissue sarcomas; and post-resection local recurrences of rectal cancer. In terms of histology, CIRT is effective for conditions that are difficult to treat with conventional radiation therapy, such as adenocarcinomas (including adenoid cystic carcinoma and hepatocellular carcinomas), sarcomas (eg, bone and soft tissue), and malignant melanomas. Furthermore, by leveraging the advantageous relative biological effectiveness and dose distribution afforded by CIRT, a number of diseases have effectively been treated with hypofractionated radiation delivery, decreasing the total time necessary for treatment. Lung and liver tumors in particular have been treated in 1 or 2 fractions; prostate cancer treatment was reduced to 12 treatments delivered in 3 weeks; and head and neck, bone and soft tissue, and recurrent rectal cancer were all treated in 16 fractions across 4 weeks. This is roughly less than half the treatment time needed in conventional radiation therapy.

On the other hand, head and neck malignant mucosal melanoma, pancreatic and cervical cancer, and other similar cancers still represent a distinct challenge because of low survival rates secondary to distant metastasis. As such, we are currently investigating combining CIRT with chemotherapy to improve treatment outcomes.
It should be noted that with respect to adverse reactions, acute effects have previously included surgery-requiring dose-dependent skin ulceration and digestive tract ulceration and perforation; however, with improvements in treatment methods, these reactions are rarely seen today. **Figure 4** shows the before and after computed tomography images of a patient treated for unresectable pelvic bone sarcoma in 1996, who is still alive today and has had no recurrence.

**Equipment Development and Future Outlook**

Up to now, we have worked on demonstrating the advantages of the heavy ion beam in treating various kinds of cancers. In light of these results, and for the sake of enabling CIRT at more locations both domestically and abroad, we have also endeavored to reduce the size and cost of the HIMAC and have succeeded in reducing both to one third that of the original machine. This prototype was installed at Gunma University in March 2010; it is operating well, and more than 1500 patients have been treated. The next model was installed at the Ion Beam Therapy Center, Saga Heavy Ion Medical Accelerator in Tosu (SAGA HIMAT) Foundation in 2013, and it has been successfully used to treat more than 800 patients to date.

Further, as opposed to merely pursuing equipment miniaturization of the first-generation HIMAC equipment, we are also developing the next generation of CIRT center, aiming to deliver respiration-synchronized rescanning beam therapy from a 360° 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, more than 700 patients have been treated with this hybrid system. In 2015, we plan to remove the range shifter entirely and transition to delivering dose using energy modulation alone.

With regard to future development of the 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. 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 installation of a normally conducting magnet, we found that the weight of the gantry could be limited to 300 tons through the use of superconducting magnets. The magnets have been produced, and gantry installation and assembly is underway; completion is planned for winter 2015. In terms of realizing new methods of radiation therapy, we expect that an even more powerful method of CIRT can be developed that does not harm healthy tissue. 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.

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 2016, while South Korea, Taiwan, and China, among others, are planning centers of their own. The NIRS is actively collaborating with these centers and nations with regard to their construction and planning processes and had signed memorandums of collaboration with a number of different institutes and universities in other countries. The US National Institutes of Health is also investigating the research potential of CIRT through the use of grants (“Planning for a National Center for Particle Beam Radiation Therapy Research,” P20 Exploratory Grant [2]), and the University of Texas Southwestern and University of California–San Francisco

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together are leading the North American Particle Therapy Alliance in investigating the development of a CIRT facility for the United States. The NIRS is actively involved with both [2]. At present, we are working on realizing an international clinical trial between the United States and Japan; recruitment for a study of CIRT on advanced pancreatic cancer in collaboration with the US National Cancer Institute has just begun [3].

Conclusions

In the past 20 years, remarkable progress has been made in the development of heavy ion radiation therapy, in terms of knowledge and delivery equipment. Simultaneously, the number of cancer patients has swelled secondary to an aging population, and society's expectation for a minimally invasive cancer treatment method capable of preserving form and function has never been higher. In this environment, CIRT is continuing to gain prominence for its use in treating cancer. 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. Japanese National Health Insurance system is currently considering whether to cover CIRT, 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.

The 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 an 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. The 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 International Atomic Energy Agency collaboration center to help disseminate CIRT technology throughout the world.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of interest: The author has no conflicts to disclose.

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