Overview of the Heavy-Ion Medical Accelerator in Chiba (HIMAC) Practices

3

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Abstract

In 1994, carbon ion radiotherapy was begun at the National Institute of Radiological Sciences (NIRS) using the Heavy-Ion Medical Accelerator in Chiba (HIMAC), which was the world's first heavy-ion accelerator complex dedicated to medical use. In the past 19 years, more than 7,000 patients have been treated with carbon ion beams at the NIRS. A total of 70 protocol studies (Phase I/II and Phase II) have been conducted to investigate the optimal indications and irradiation techniques. Hypo-fractionated carbon ion radiotherapy protocols (average: 13 fractions per patient) with acceptable morbidities have been established for various types of tumors. Carbon ion therapy is associated with improved local control and survival in radioresistant advanced tumors such as sarcomas, melanomas, and other non-squamous cancers. The next-generation carbon ion therapy system has been under development to realize more advanced techniques, such as respiration-gated 3-D active beam scanning with a compact rotating gantry with superconducting magnets.

Keywords

HIMAC • Hypo-fractionated • Protocol studies

3.1 Introduction

In Japan, the decision to implement the medical use of heavy ions was made in 1984 as one of the main projects of the first comprehensive 10-year strategy for cancer control. The Heavy-Ion Medical Accelerator in Chiba (HIMAC) was the world's first heavy-ion accelerator complex dedicated to clinical research. The accelerator complex took almost 10 years to design and construct and was completed at the end of 1993. After 6 months of commissioning of the facility, clinical trials using carbon ion beams generated from the HIMAC were initiated in June 1994. This chapter will provide an overview of carbon ion radiotherapy over the last 19 years at the National Institute of Radiological Sciences (NIRS).

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3.2 The HIMAC

The design parameters of the HIMAC were based on the estimated radiological requirements. Ion species ranging from He to Ar can be accelerated to the desired energies. The beam energy was designed to vary from 100 to 800 MeV/u for efficient treatment. The HIMAC consists of an injector linear accelerator (linac) cascade, dual synchrotron rings with independent vertical and horizontal beam lines, and three treatment rooms equipped with passive beam delivery systems.

For carbon ion radiotherapy, a C^{2+} beam produced by the 10 GHz-ECR ion is injected into the linac cascade consisting of RFQ and Alvaretz linacs and is accelerated up to 6 MeV/n. After the carbon beam is fully stripped with a carbon-foil stripper, the beam is then injected into the synchrotron rings by a multiturn-injection scheme and is slowly extracted after acceleration to a desired energy. Finally, the carbon beam extracted from the synchrotron is delivered via the beam

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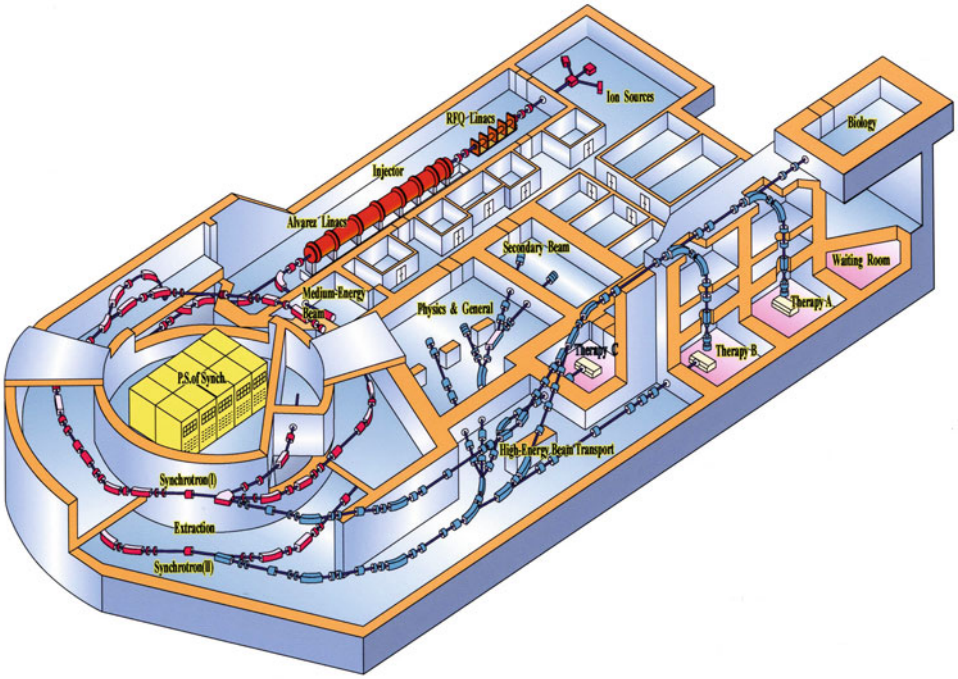

Fig. 3.1 A bird's-eye view of the HIMAC facility A unique double-synchrotron ring heavy-ion accelerator system dedicated for medical use was designed and constructed. It consists of two ion sources, an RFQ (radio frequency quadrupole) linear accelerator (linac), an Alvarez linear accelerator (linac), two synchrotron rings, a high-energy beam transport system, and an irradiation system

delivery system [1, 2]. A bird's-eye view of the HIMAC facility is shown in Fig. 3.1, and the specifications of the HIMAC are listed in Table 3.1. The footprint of the HIMAC was 120×65 m, and its construction cost reached to 32,600,000,000 JPY.

In order to conform the dose to a specific target, a passive beam delivery technique has been employed. The beam lines in the treatment room are equipped with a pair of wobbler magnets, beam scatterers, ridge filters, multi-leaf collimators, and the ability to administer a compensation bolus. An appropriately designed ridge filter, which corresponds to and determines the size of the spread out of Bragg peak (SOBP), is chosen to avoid unnecessary dosing of normal tissues along the beam path in each port. Twelve different size ridge filters were made to cover thicknesses of 2–15 cm.

The patients are positioned in customized cradles and immobilized with a low-temperature thermoplastic cast. A set of CT images are taken for treatment planning with the immobilization devices in place. Respiratory gating for both the CT acquisition and therapy is performed when indicated [3]. A three-dimensional treatment planning is performed using our original HIPLAN software program, which was developed for carbon ion radiotherapy CIRT [4]. A margin of 5 mm is usually added to the clinical target volume to create the planning target volume. The dose is calculated for the target volume and any nearby critical structures and expressed in Gray-equivalents (GyE = carbon physical dose in Gray × Relative Biological Effectiveness {RBE}).

Radiobiological studies were carried out in mice and in five human cell lines cultured in vitro to estimate RBE values relative to megavoltage photons. Irrespective of the size of the SOBP, the RBE value of carbon ions was estimated to be 3.0 at the distal part of the SOBP, and ridge filters were designed to produce a physical dose gradient of the SOBP so that the biological effect along the SOBP became uniform. This was based on the biologic response of human salivary gland tumor cells at a 10 % survival level. The biological response flatness along the SOBP was checked by measuring the physical dose distributions and dose-averaged LET, which were in satisfactory agreement with the calculated results [5].

Carbon ion radiotherapy (C-ion RT) is given once daily, 4 day/week (Tuesday to Friday). During every treatment session, the patient's position is verified with a computer-aided online positioning system.

A new beam delivery with active scanning was started in May 2011, and we have since treated more than 200 patients with fixed targets.

Table 3.1 Specifications of the HIMAC

Ion: H–Ar	
Max energy	100–800 MeV/u
Treatment room [3]	
Fixed vertical	Room A
Fixed horizontal	Room C
Fixed vertical and horizontal	Room B
Accelerated energy	
Vertical beam	140 or 290 or 350 or 400 MeV/u
Horizontal beam	140 or 290 or 400 or 430 MeV/u
Range of carbon ion beam in water	
140 MeV/u	5 cm
290 MeV/u	15 cm
350 MeV/u	20 cm
400 MeV/u	25 cm
430 MeV/u	30 cm
Maximum field size	15 cm by 15 cm

3.3 Clinical Trials at the NIRS

From June 1994 until March 2013, a total of 70 protocols were conducted in an attempt to determine the optimal dose-fractionation and irradiation method for the treatment of specific diseases. The HIMAC passive beam delivery system has been showing reliable and stable performance for the last 19 years, and a total of more than 7,000 patients had been registered for treatment, and the C-ion RT was approved as a clinical practice in 2003. The number of patients treated as part of clinical practice as of June 2013 has been more than 4,000 at the NIRS (Fig. 3.2). The categories of disease that can be treated in routine clinical practice include lung cancer, prostate cancer, head and neck cancer, skull base tumors, ocular melanoma, bone and soft tissue sarcoma, liver cancer, pelvic recurrences of rectal cancer, pancreatic cancer, uterine cervical cancer, and re-irradiation after conventional radiotherapy, among others. The number of patients has increased every year, and the facility has reached a capacity permitting more than 800 patients to be treated each year (Fig. 3.3).

The clinical trials began with a small dose per fraction. At first, the average number of fractions was around 18. All these early trials were carried out as dose-escalation studies. It was found that a very high dose per fraction could be administered because of the better dose distribution of carbon ion beams. In addition to the high physical selectivity of carbon ion beam, the biological properties associated with the high-LET carbon beam, low DNA repair, cell cycle non-specific activity, and low OER are well-known effects that facilitate cancer eradication. Hence, a protracted fractionated regimen is not advantageous in carbon therapy. Therefore, we started performing less fractionated or hypo-fractionated radiotherapy. When using such treatments, the overall treatment time should be shorter, and the effect of repopulation is limited. The average number of fractions could subsequently be reduced from 18 to 12–13. Over the last several years, this reduction of fraction number has led to remarkable improvements in patient throughput at the NIRS (Fig. 3.4).

The clinical results in the most common sites of cancer at the NIRS are briefly summarized below:

1. Head and Neck Cancers
   Carbon ion radiotherapy was first applied for the treatment of patients with unresectable locally advanced head and neck tumors. A dose-escalation study using 18 fixed fractions delivered over 6 weeks was conducted and then shortened to 16 fractions over 4 weeks' schedule. More than 800 locally advanced tumors were treated in head and neck protocols with this protocol, with the total dose being either 57.6 or 64 GyE. The treatment results obtained so far can be summed up by stating that a very favorable local control rate of around 80 % has been achieved, mainly for adenocarcinoma, adenoid cystic carcinoma, and mucosal malignant melanoma. With regard to malignant melanoma, however, a combined regimen of carbon ion radiotherapy and chemotherapy was initiated in order to better control or prevent distant metastasis. For sarcomas arising from head and neck region, a total dose of 70.4 GyE was required to achieve a similar local control rate.
2. Lung Cancer
   Patients with medically inoperable stage I non-small cell lung cancer were treated under several protocols. We started with fixed 18 fractions over 6 weeks' dose-escalation study and then shortened the overall treatment time to 3 weeks in two protocols. The results of these studies were better than those of conventional radiotherapy and almost the same as those of surgery. We have beeen conducting a fixed four fractions over 1 week protocol since 2000. We are able to give a very high dose in 1 week without unacceptable side effects. A single fraction dose-escalating study was started in 2003, and the dose was increased from 28 to 50 GyE in more than 200 patients. A total of more than 400 patients with stage I non-small cell lung cancer have been enrolled in these protocols. The results are quite promising, including those of the single fraction study that have been reported so far. To clarify the best regimen for stage I non-small cell lung cancer, a randomized controlled clinical trial comparing different fractionations could be conducted.
3. Liver Cancer
   For primary liver cancer, 15 fractions over 5 weeks' irradiation schedule were employed initially. The overall treatment time of 5 weeks then was shortened to 3, 2, and 1 week and then to 2 days in the subsequent studies. The shortest irradiation schedule of two fractions/2 days has been showing encouraging results in terms of a favorable local control rate and the absence of any particular serious

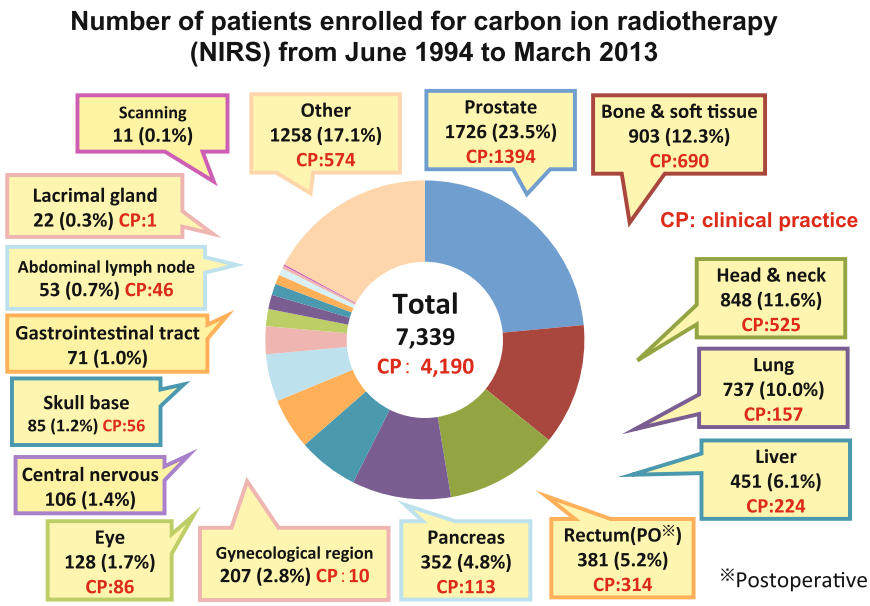

Fig. 3.2 The number of patients treated using carbon ion radiotherapy from June 1994 to March 2013 at the NIRS. A total of 7,349 patients had received carbon therapy at the NIRS as of March 2013. Prostate cancer, sarcoma, head and neck cancer, lung cancer, liver cancer, postoperative local recurrence of rectal cancer, and pancreatic cancer were the most frequently treated tumors at the NIRS. More than 4,000 patients have received carbon ion radiotherapy as part of clinical practice

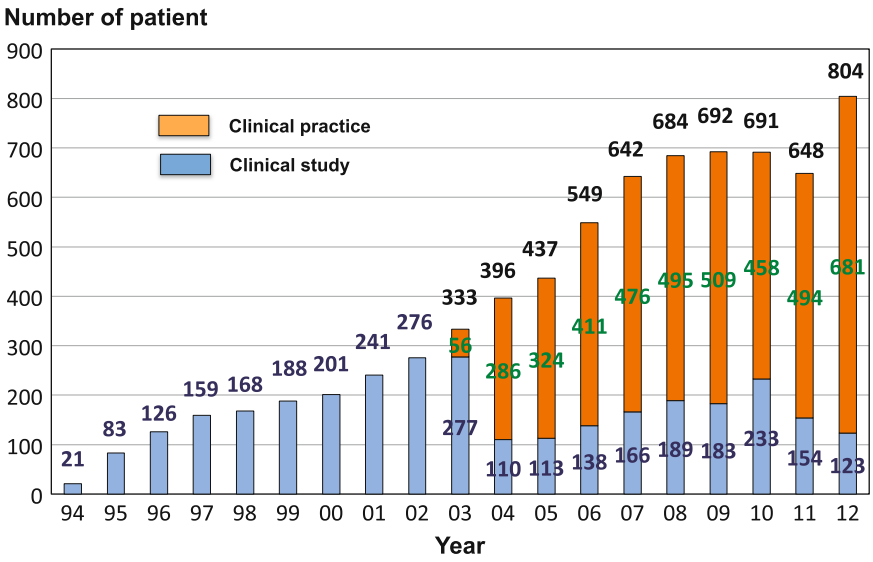

Fig. 3.3 The annual patient accrual at the NIRS. Carbon ion radiotherapy has been performed as part of clinical practice with government approval since 2003. The cost of carbon ion treatment as part of clinical practice is 3,140,000 JPY per case, irrespective of the fraction number. However, the number of patients has been increasing every year, and in 2012, 804 patients were registered for treatment at the NIRS

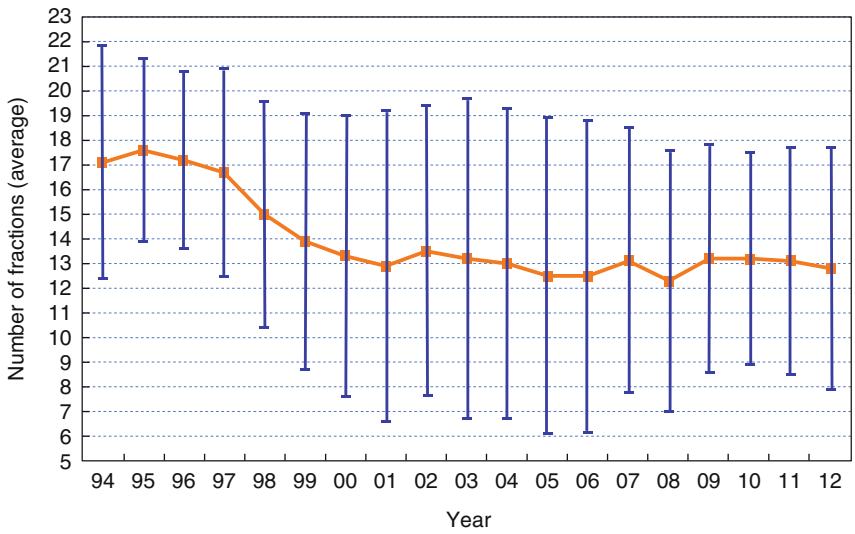

Fig. 3.4 The average fraction number per case. The average number of fractions administered at the beginning was almost 18 and has since then been reduced to 13. The reduction has mainly been achieved by implementing hypo-fractionation protocols. This reduction of the fraction number per patient not only improves the outcome for patients, but also increases the number of treatment slots at the NIRS

toxic reactions even in patients with a large (5 cm or more in diameter) tumor. Nearly 450 patients were treated with carbon beams. A single fraction dose-escalation study for metastatic liver cancer, which is associated with a better liver function compared to primary liver cancer, is currently ongoing.

4. Pancreatic Cancer
   Pancreatic cancer is rarely curable, and because of its location, it causes significant symptoms such as intractable back pain and gastrointestinal obstruction. The 5-year survival rate achieved with surgical resection is generally unfavorable, at less than 20 %. In the case of locally advanced unresectable cancer of the pancreas, the 2-year survival rate is even lower. In order to improve the treatment results for cancer of the pancreas, the critical factor is how effectively liver metastasis and retroperitoneal recurrence are controlled, since these account for 50 % of all recurrences. Attempts have been made to improve the local efficacy first and to establish therapeutic strategies involving the concomitant use of chemotherapy with C-ion RT. At present, a clinical trial of short-course preoperative carbon beam irradiation is in progress.

   For locally advanced unresectable pancreatic cancer, a dose-escalation clinical trial of 3 weeks of concurrent chemo-carbon ion irradiation was conducted, and a dramatic improvement of the 2-year overall survival rate was observed, without severe morbidities, in the high-dose group.
5. Rectal Cancer (Postoperative Pelvic Recurrence)
   Although the incidence of postoperative rectal cancer recurrence in the pelvis has decreased as a result of improvements in surgical procedures, the incidence of recurrence after surgery is still almost 20 %. Many of the patients with local recurrence are not eligible for surgical resection and are frequently referred for radiotherapy. However, the results are far from adequate. Many of the previous reports have documented a 50 % survival period of 12 months and a 3-year survival rate of around 10 %, and the role of radiotherapy is often described as palliative. Almost 400 patients have so far been treated with carbon ion radiotherapy, and no serious toxic reactions have been observed. The results, in terms of the local control and survival rates, have been favorable in comparison with conventional radiotherapy and are comparable to those achieved with surgery.
6. Prostate Cancer
   A total of three clinical trials have so far been carried out in patients with prostate cancer. The first carbon ion radiotherapy trial (20 fixed fractions over 5 weeks) with concomitant endocrine therapy was conducted for B2-C stage patients. The second trial had a wider scope of eligibility and consisted of carbon ion monotherapy for stage A2-B1 prostate cancer and C-ion RT combined with endocrine therapy for stage B2-C. In the first clinical trial, the most serious toxicities in the rectum were recorded among the patients exposed to the highest dose. As a result, a safe dose for the digestive tract was established, and no serious toxic reactions were subsequently encountered in the later clinical trials. A total dose of 63 GyE was found to be the optimal dose for the 20 fractions over 5 weeks' protocol. The overall treatment time was then shortened to 4 weeks and showed better outcomes. After that we conducted a study of 12 fractions over 3 weeks in 2010. There were no severe side effects, and since April 2013, all prostate cancers were treated with the 3 weeks regimen. The total number of prostate cancers treated with carbon ion is now nearly 1,800.
7. Bone and Soft Tissue Sarcomas
   Bone and soft tissue sarcomas are generally considered to be radioresistant. Advanced tumors originating in the trunk, in particular, are often not resectable and have a poor prognosis. The use of carbon ion beams offers a favorable prospect of improved local control in view of its superior biological dose distribution. The patients enrolled in our initial dose-escalation trial were primarily subjects who had not successfully responded to surgery or were totally inoperable. This trial has produced favorable local control, and it showed that chordoma and osteosarcoma are prime candidates for C-ion RT. Some 10 % of the patients whose lesions are close to the body surface, making it impossible to avoid exposure of the skin to high radiation doses, developed severe reactions, such as skin ulceration. As more experience has been gained and significant improvements in irradiation techniques have been achieved, such severe reactions no longer occur. Bone and soft tissue tumors in the trunk are the most typical lesions qualifying for carbon ion radiotherapy, and 900 such patients have been treated so far.

3.4 Future Prospects of Carbon Ion Radiotherapy at the NIRS

Our clinical experience has demonstrated the superiority of carbon ion beams over other types of irradiation for the treatment of various tumors. The current facilities and devices may be termed the "first-generation" equipment for carbon ion radiotherapy. It is important to develop advanced second- and third-generation equipment to bolster international competitiveness, because many countries are starting to establish new medical facilities for carbon ion radiotherapy. Mere downsizing of the treatment equipment will be far from satisfactory.

One new technique that deserves particular attention is the 3-D scanning beam delivery method, which uses "narrow" pencil beams of carbon ions to cover an entire target volume. The NIRS has been conducting extensive research

and development projects for the clinical application of the 3-D scanning. We have successfully developed a 3-D active scanning method that can treat fixed targets, although this method has not yet been put into practice for the treatment of a moving target with respiration (as of June 2013).

Active 3-D beam delivery is appropriate for the treatment of complex-shaped lesions that cannot be adequately irradiated by the passive beam delivery. It will also adapt treatment to time-course changes in the target shape. The current treatment procedure for prostate cancer requires 12 fractions over 3 weeks. The number of fractions can possibly be reduced by applying the 3-D scanning technique, since it can reduce the dose to the urethra, which is the most serious organ at risk, because it runs through the middle of the prostate gland. The use of a rotating gantry will minimize the time required for patient positioning and the patient's physical burden during irradiation. For example, in the case of a patient with lung cancer, the current system using fixed beam lines requires 1.0–1.5 h per session with four different angle irradiations for single fraction treatment. The new system will reduce this to 30 min, because the session will not require repositioning of the patient. In addition, the new system may be applicable for patients with a poor general condition, owing to its simplified treatment setup procedures and reduced treatment time.

We anticipate that the introduction of the 3-D scanning technique and the rotating gantry will not only improve the therapeutic outcome but also dramatically increase the number of patients who can be treated (due to expanded indications and a higher treatment efficiency, as well as the shorter duration of treatments).

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