

## Carbon Ion Radiotherapy: Clinical Experiences at National Institute of Radiological Science (NIRS)

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### Heavy particles/Carbon ion radiotherapy/Hypofraction/Review.

In June 1994, the world's first clinical center offering carbon ion radiotherapy opened at the National Institute of Radiological Science (NIRS), Japan. Among several types of ion species, carbon ions were chosen for cancer therapy because they were judged to have the most optimal properties in terms of superior physical and biological characteristics. As of March 2010, 5,196 patients have been registered for carbon ion radiotherapy. Clinical results have shown that carbon ion radiotherapy has the potential to provide a sufficient radiation dose to the tumor, while having acceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to carbon ions include locally advanced tumors as well as histologically non-squamous cell tumor types such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. By taking advantage of the unique properties of carbon ions, treatment with small fractions within a short treatment period has been successfully carried out for a variety of tumors. This means that carbon ion radiotherapy can offer treatment for larger numbers of patients than is possible with other modalities over the same time period.

### INTRODUCTION

Charged particle radiotherapy using protons and heavier ions was first proposed for clinical application by Robert Wilson in 1946.<sup>1)</sup> In the early 1950s, the clinical use of proton and helium ion beams was initiated at the Lawrence Berkeley National Laboratory in the United States. This paved the way for heavy ion beam radiotherapy starting at the same facility in the 1970s.<sup>2,3)</sup> The proton accelerator built at Loma Linda University in 1990 was the first proton beam accelerator used primarily for therapeutic service. At present, particle beam radiotherapy is being performed at about 30 facilities around the world, and many more are under construction or in the planning stage.<sup>4)</sup>

In Japan, the decision was made in 1984 to build the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the

National Institute of Radiological Science (NIRS) as an integral part of the nation's "Overall Ten-year Anti-Cancer Strategy". The accelerator complex took almost a decade to build, being completed by the end of 1993. A year later, clinical study with carbon ions for cancer therapy was initiated. HIMAC can claim to be the world's first facility dedicated to cancer therapy using carbon ion beams. HIMAC has also been operated as a multipurpose facility for both cancer treatment and biological, physical research.

Carbon ion radiotherapy now enters its 15<sup>th</sup> year at NIRS. A substantial amount of evidence supporting the clinical efficacy of carbon ions to treat various tumor types has been accumulated by many contributing members both inside and outside the Institute. One of the most important objectives in these endeavors has been to confirm, in particular, the validity of hypofractionated and accelerated radiotherapy. In November 2003, the Ministry of Health, Labor and Welfare in Japan approved carbon ion radiotherapy as "Highly Advanced Medical Technology (HAMT)" under the title of "Carbon Ion Radiotherapy for Solid Cancer". HAMT is designed to respond to the development of new medical technologies and to meet the diversifying needs for advanced treatment. In this manner, heavy particle radiotherapy has earned a solid place in general medical practice. The next target is the

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approval of this therapy by the National Health Insurance System in Japan.<sup>4)</sup>

This article reviews the clinical results of carbon ion radiotherapy over the last decade at NIRS.

**CHARACTERISTICS OF CARBON ION BEAMS**

*Physical Aspects*

Unlike X-rays, which deposit most of their energy near the skin surface, particle beams, such as proton and heavier ion beams, show an increase in energy deposition as depth increases. The penetration depth of these beams achieves a sharp maximum at the end of their range to form the so-called Bragg peak. Beyond the Bragg peak, almost no dose is deposited in normal tissue.<sup>5)</sup> In addition, ion dose localization in the tumor improves as the peak-to-plateau ratio rises. In this respect, carbon ion radiation is particularly outstanding because its peak-to-plateau ratio is larger than any other ion beams under certain conditions.<sup>6)</sup>

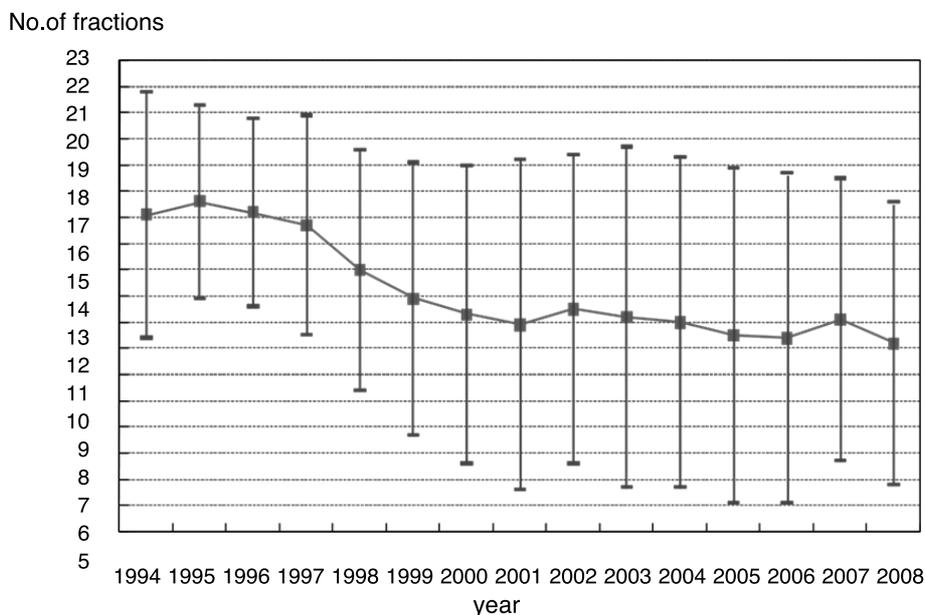
Carbon ions are accelerated to 800 Mev/nucleon (83% of light velocity) by major synchrotrons, and at HIMAC the resulting beams can penetrate as deep as 30 cm in water. For modulation of the Bragg peak to conform to a target volume, the beam lines for treatment are equipped with a pair of wobbler magnets, beam scatterers, ridge filters, multileaf collimators, and compensation bolus. The ridge filter is designed to produce biologically equal effects throughout the spread-out Bragg peak (SOBP). The compensation bolus is fabricated for each patient so that the distal configuration of the SOBP is similar to any irregular shape of the target volume with the collimator used to define the lateral outline.

Favorable dose distributions will have a steep dose fall-off at the field borders. As a consequence, more precise dose localization can be achieved with carbon ion beams compared to photon beams.<sup>6)</sup>

*Biological Aspects*

Carbon ions cause a different type of cellular damage than do protons and photons and deliver a larger mean energy per unit length (Linear Energy Transfer: LET) of their trajectory in the body.<sup>7)</sup> This unique property provides high local tumor control when used in radiotherapy. Carbon ions directly cleave double-stranded DNA at multiple sites even at low oxygen content, which allows access to hypoxic parts of tumors that would be resistant to low LET radiotherapy. As a result, carbon ion beams are described as high-LET radiation and are similar to neutron beams. The LET of neutron beams remains uniform at any depth in the body. However, the LET of carbon ion beams increases steadily from the point of incidence in the body with increasing depth to reach a maximum in the peak region. This property is extremely advantageous from a therapeutic viewpoint in terms of increased biological effect on the tumor. The reason is that carbon ion beams form a large peak in the body, as their physical dose and biological effectiveness increases as they advance to the more deep-lying parts of the body. This quality of carbon ion beams provides promising potential for their highly effective use in the treatment of intractable cancers that are resistant to photon beams.<sup>8)</sup>

In view of these unique properties of carbon ion beams, it is theoretically possible to perform hypofractionated radiotherapy using significantly smaller numbers of frac-



**Fig. 1.** Average Number of Fractions in Carbon Ion Radiotherapy.

tions than have been used in conventional radiotherapy. Experiments conducted with fast neutrons have demonstrated that increasing the dose per fraction tends to lower the relative biological effectiveness (RBE) of both tumor and normal tissues.<sup>9)</sup> The RBE of the tumor, however, did not decrease as rapidly as the RBE of normal tissue.<sup>10,11)</sup> This experimental result substantiates the fact that the therapeutic ratio increases rather than decreases even though the fraction dose is increased. At NIRS, hypofractionated carbon ion radiotherapy has been investigated systematically for a variety of tumor entities. The use of these properties makes it possible to complete the therapy in a short time without enhancing toxicity. At present, the average number of fractions and treatment time per patient at NIRS is 12.5 fractions and 3 weeks, respectively (Fig. 1).

### CLINICAL RESULTS OF CARBON ION RADIOTHERAPY

Carbon ion radiotherapy at NIRS was initiated in June 1994.<sup>12)</sup> To date, more than 60 protocols have been established, and phase I/II and II trials have been conducted in an attempt to determine the optimal dose-fractionations and irradiation techniques for each specific tumor.<sup>13-15)</sup> The number of patients has increased during ongoing years, and the facility has now reached a capacity that permits almost 700 cases to be treated annually. As of March 2010, 5,196 patients have been registered (Fig. 2). The categories of disease that can be treated in the HAMT scheme include skull base tumor, head and neck cancer, lung cancer, prostate cancer, bone and soft-tissue sarcoma, liver cancer, pelvic recur-

rences of rectal cancer, and choroidal melanoma (Fig. 3). By pathological type, carbon ion radiotherapy is effective against non-squamous cell types of tumors for which photon beams are minimally effective, including adenocarcinoma, adenoid cystic carcinoma, hepatocellular carcinoma, and sarcomas (malignant melanoma, bone and soft-tissue tumors, etc.).

The treatment details for each tumor are described in the

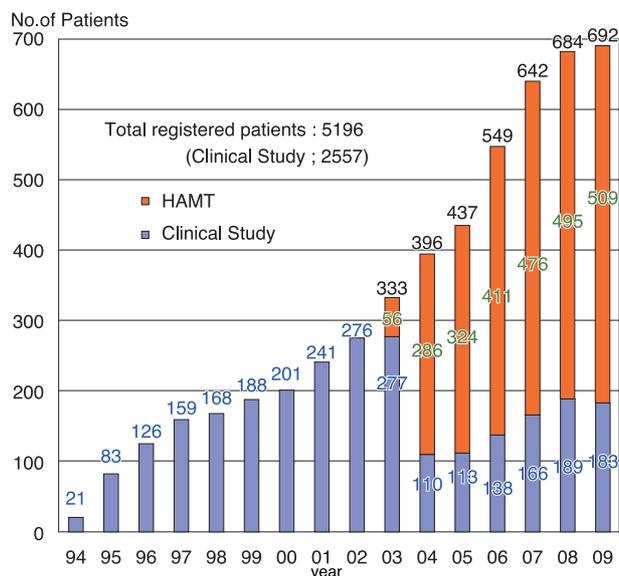


Fig. 2. Number of Patients registered in Carbon Ion Therapy at NIRS (Period: June 1994- March 2010). HAMT: Highly Advanced Medical Technology.

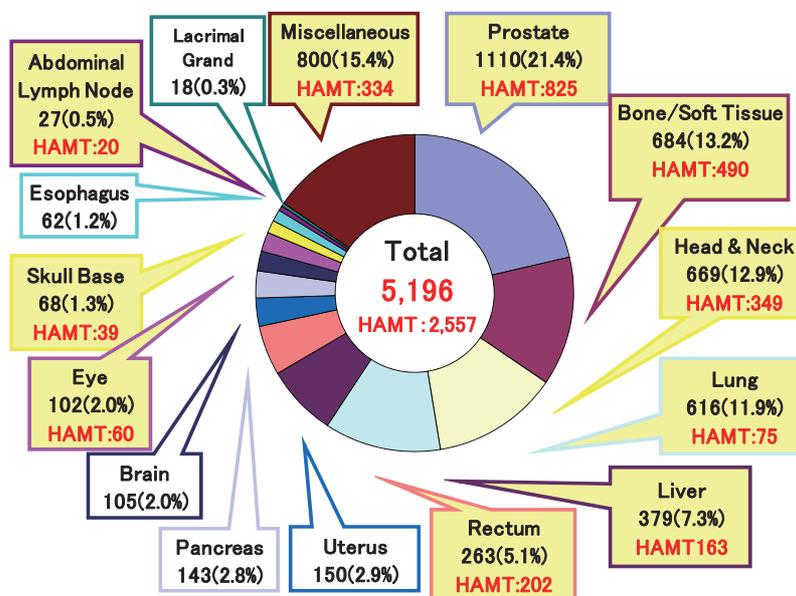


Fig. 3. Number of Patients registered in Carbon Ion Therapy at NIRS (Period: June 1994–March 2010). HAMT: Highly Advanced Medical Technology.

subsequent sections. In principle, toxicity was evaluated according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) criteria or National Cancer Institute-Common Toxicity Criteria (NCI-CTC), and local control and survival rates were calculated by Kaplan-Meier estimation.

## COMMON CANCERS

### *Non-Small Cell Lung Cancer (T1-2N0M0)*

Stage I lung cancer is divided into two groups according to tumor location: peripheral-type and central-type. This classification is made on the assumption that, as the central-type tumor is located closer to major bronchi than the peripheral-type tumor, the two may tolerate radiation differently. Thus, different fractionation regimens should be investigated for each. The patients eligible for either treatment are those for whom surgery was not indicated due to medical reasons or refusal.

For peripheral-type, a phase I/II clinical trial was conducted with 18 fractions/6 weeks and 9 fractions/3 weeks from 1994 to 1999. The results achieved good local control with minimal pulmonary damage. The optimal dose and fractions were determined as 72.0 GyE in 9 fractions over 3 weeks. In the phase II study, 50 patients were treated using this optimal schedule. There were no serious toxic reactions. The 5-year local control rate was 94.7%, with an overall survival rate of 50% (the corresponding the cause-specific survival rate was 75.7%).<sup>16)</sup>

Moreover, the fraction number and treatment time were reduced in gradual steps to 52.8 GyE for stage IA and 60.0 GyE for stage IB in 4 fractions/1 week. In this phase II study, 79 patients were treated. The 5-year local control rate was 90%, with a cause-specific survival rate of 68%, and an overall survival rate of 45%. Half of the deaths were attributed to intercurrent diseases. No toxic reactions in the lung greater than grade 3 were detected.<sup>17)</sup>

The dose-escalation study with single-fraction treatment was initiated in April 2003. The initial dose was 28.0 GyE, with the total irradiation dose being escalated in increments of 2.0 GyE, up to 44.0 GyE. The preliminary data suggest favorable local control and very few toxic reactions with a median follow up time of about 16 months. For skin reactions, only one grade 2 toxicity was reported, and no grade 3 or higher was observed. For radiation pneumonitis, only one grade 1 was reported, and no toxicities greater than grade 2 occurred.<sup>18)</sup> Compared with pulmonary damage reported for stereotactic radiotherapy to treat stage I lung cancer,<sup>19-21)</sup> the incidence and severity in our patients seemed to be remarkably low. The decreased adverse effects on the lung were likely achieved due to the small volume irradiated. This single-fraction irradiation method may be described as the ultimate type of treatment using carbon ion,

and would be a valid alternative to surgery, especially for elderly and inoperable patients. This clinical trial is still in progress.

For the treatment of central-type lung cancer, a larger fraction number than for the peripheral-type was used. For a central-type forming a bulky lesion, higher doses than those used for the peripheral type should be employed. A phase I/II study was initiated using 12 fractions over 3 weeks. In order to avoid serious toxic reactions for hilum including main bronchus, the dose was set at 68.4 GyE. This trial is still ongoing, with early encouraging local control and acceptable toxicities.

### *Hepatocellular Carcinoma*

Clinical studies were carried out on four protocols for hepatocellular carcinoma (HCC) between April 1995 and August 2005. Eligibility criteria of these protocols were patients for whom other therapies offered no potential of sufficient efficacy or who had treatments that were ineffective for local tumor control. In the first phase I/II dose escalation study, 24 patients were treated with a total dose ranging from 49.5 GyE to 79.5 GyE in 15 fractions over 5 weeks. Both 3- and 5-year local control rates were 81%.<sup>22)</sup> In the second phase I/II study, successive dose escalation was implemented from 12 fractions/3 weeks through 8 fractions/2 weeks to 4 fractions/1 week. All of these fractionation regimens resulted in acceptable toxicities. Based on these results, a phase II study was initiated using a recommended dose of 52.8 GyE in 4 fractions over 1 week. The total number of patients treated with four fractions in the second and third clinical studies was 75. In these patients, post-treatment impairment in hepatic function was minimal, and the 5-year local control and survival rates were recorded as 94% and 33%, respectively.<sup>23)</sup> The fourth clinical study using an even shorter irradiation schedule of 2 fractions in 2 days was conducted from April 2003 to August 2005, with encouraging results for both a favorable local control rate and the absence of particularly serious toxic reactions.<sup>24)</sup> The preliminary data for 2 fractions toxicity showed a very low rate. For skin reaction, no grade 2 or higher was observed. For liver function, three of grade 2 were reported, and no toxicities greater than grade 3 occurred. This two-fractionated treatment is now being used under HAMT. Large lesions of 3 cm or more are difficult to treat with percutaneous ethanol injection or radio-frequency ablation alone, making them ideal targets for carbon ion radiotherapy. Patients having locally concentrated lesions over 3 cm and up to 5 cm are particularly suited for carbon ion radiotherapy.<sup>25)</sup> We have recently added four-dimensional CT in order to calculate internal target volume when the tumor was located close to critical organs such as the spinal cord or bowel.

### *Prostate Cancer*

To establish an appropriate dose fractionation regimen for

carbon ion radiotherapy of prostate cancer, two phase I/II studies have been performed since 1994.<sup>26,27)</sup> A phase II clinical study was started in April 2000 with the recommended dose of 66.0 or 63.0 GyE in 20 fractions over 5 weeks.<sup>28)</sup> The safety and efficacy of this treatment strategy of carbon ion radiotherapy was further confirmed with this phase II study, which was approved for HAMT. In this study, the patients were divided into high-risk and low-risk groups on the basis of various pre-treatment factors (PSA, Gleason score, and TNM classification). The high-risk group received combined carbon ion radiotherapy and hormonal therapy, while the low-risk group was treated with carbon ion radiotherapy alone. We started to treat all new patients with a more hypofractionated schedule of 57.6 GyE/16 fractions in September 2007.

So far, a total of 1110 patients have been treated with carbon ion radiotherapy, and 825 under HAMT. Of this total, 740 patients received the established treatment of carbon ion radiotherapy, and were followed up for at least 6 months. The 5-year overall and biochemical relapse free (bNED) survivals were 95.4% and 90.2%, respectively.<sup>29)</sup> Furthermore, the 5-year bNED of 16 fractions also had comparable results compared with 20 fractions.

In the first dose escalation study, grade 3 toxicities in the rectum were reported among severely diabetic patients exposed to the highest total dose of 72.0 GyE. As a result, a dose tolerable for the rectum was established and no serious toxic reactions were subsequently encountered in later clinical studies. Dose volume histogram (DVH) analysis was also performed to identify the tolerance dose of the rectum, using a rectal DVH curve that permits prediction of the risk of rectal reactions. This curve has made it possible to easily prevent severe rectal reactions in new patients at the time of treatment planning. Using this method, no grade 3 or higher toxicities were observed in the rectum even for the patients with severe diabetes. In the 664 patients treated with either 66.0 or 63.0 GyE/20 fractions or 57.6 GyE/16 fractions, and followed up more than 12 months, the incidence of grade 2 rectum and genitourinary (GU) morbidity was only 1.9% and 4.8%, respectively. In addition, the incidence of grade 2 rectum morbidities at 66.0 GyE/20 fractions, 63.0 GyE/20 fractions, and 57.6 GyE/16 fractions were 3.2%, 1.9%, and 1.0%, respectively, while grade 2 GU morbidities were 8.4%, 3.7%, and 1.5%, respectively.<sup>29)</sup>

These results substantiated the validity of our hypofractionated regimen. Our results show that it is possible to accomplish carbon ion radiotherapy in 16 fractions over 4 weeks, which is only half the fractions and time employed by most intensity modulated radiation therapy and proton beam therapies. More recently, a new clinical trial using an even shorter irradiation schedule of 12 fractions over 3 weeks has been started.

### *Rectal Cancer (post-operative pelvic recurrence)*

Although postoperative rectal cancer recurrence in the pelvis has decreased as a result of improvements in surgical techniques, its incidence is still in a range of 10 to 40%.<sup>30-32)</sup> Many of the patients with local recurrence are not eligible for surgical resection and are frequently referred for radiotherapy. However, the results of conventional photon radiotherapy are still far from satisfactory, with many studies in the literature reporting a 50% survival period of 12 months and a 3-year survival rate of around 10%. The role of photon radiotherapy is often described as mere pain control.

The phase I/II study for locally recurrent rectal cancer was performed in April 2001. All patients had potentially curative resection of the primary tumor regardless of surgical procedures with local recurrence without distant metastasis confirmed by several diagnostic imaging techniques, including positron emission tomography. Those having the digestive tract in contact with the clinical target volume were excluded. So far, 105 patients have been treated with carbon ion radiotherapy. No particularly serious toxic reactions have been observed. None of the 75 patients treated with the highest total dose of 73.6 GyE experienced NCI-CTC grade 3 - 5 acute reactions. The overall local control rate was 92% at 3 years. The median survival time was 54 months (range 7 - 52 months), and the 3- and 5-year overall survival rates were 71% and 39%, respectively. Carbon ion radiotherapy for locally recurrent rectal cancer is an effective local treatment, and could represent a promising alternative to surgery.<sup>33)</sup>

### *Pancreatic Cancer*

Adenocarcinoma of the pancreas is the fifth leading cause of cancer-related deaths in Japan, resulting in approximately 19,000 deaths a year. The 5-year survival rate achieved with surgical resection is unfavorable at less than 20%. In the case of locally advanced unresectable cancer, the 2-year survival rate is even lower at only about 10%. To improve the treatment results, the critical factor lies in how to effectively prevent or control liver metastasis as well as retroperitoneal recurrence that accounts for 50% of all recurrences.

In carbon ion radiotherapy, attempts have been made to improve local efficacy first, and then to establish therapeutic strategies involving concomitant use of chemotherapy. In June 2000, the first clinical study on preoperative carbon ion radiotherapy was started with 16 fractions in 4 weeks. Twenty-two patients were enrolled, judged by staging criteria of the Japanese Committee on Cancer as clinical stages I, II, III or IVa, and equivalent stages I, II or III by the TNM staging criteria. The overall local control rates at the primary tumor bed were 100% at 1 year and 87% at 2 years. One local failure was observed in the residual pancreas at 18 months after pancreaticoduodenectomy. The 2-year overall survival rates were 24% for all patients including 7 patients having unresectable cancer and 36% for the resected group, respectively.

These results have led to a second study of preoperative irradiation with 8 fractions in 2 weeks. At present, patient enrollment in the trial is in progress, and the outcomes are pending. Early data indicate a higher level of survival rates than the first protocol.

In the dose-escalation study on carbon ion radiotherapy alone for locally advanced pancreatic cancer, 31 patients with clinical stage IVa or IVb and without distant metastasis were enrolled. Carbon ion radiotherapy was given in 12 fractions over 3 weeks. The dose was set at 38.4 GyE and escalated to 48.0 GyE at 5% increments. All patients completed the scheduled treatment course and toxicities were all within acceptable levels. The overall local control rate and survival rate at one year were 81% and 44%, respectively.

These results suggest the potential benefit of carbon ion radiotherapy compared to conventional photon radiotherapy. In addition, gemcitabine has a sensitizing effect in conjunction with heavy particle beams as demonstrated in *in vitro* studies.<sup>34)</sup> A new phase I/II study of gemcitabine-combined carbon ion radiotherapy for locally advanced pancreatic cancer was started in April 2007. The dose of carbon ion radiation was first fixed at 43.2 GyE/12 fractions/3 weeks, and the dose of gemcitabine was escalated from 400 mg to 1000 mg/m<sup>2</sup>; the dose of gemcitabine was then fixed at 1000 mg/m<sup>2</sup> and the dose of carbon ion radiation was escalated from 45.6 GyE to 50.4 GyE. Gemcitabine was given once weekly on days 1, 8, and 15. It is remarkable that current carbon ion radiotherapy may enable patients to tolerate full dose gemcitabine (1000 mg/m<sup>2</sup>) without severe gastrointestinal side effects, which is in contrast to photon radiotherapy. More recently, the dose of 48.0 GyE /12 fractions /3 weeks has been employed with full dose gemcitabine. This trial is still ongoing with early encouraging survival and acceptable toxicities.<sup>35)</sup>

### *Esophageal Cancer*

Currently, a protocol for preoperative carbon ion radiotherapy is being carried out for esophageal cancer. Its purpose is to improve the survival rate by using short-course carbon irradiation, with plans for future use with combined chemotherapy. After preoperative carbon ion radiotherapy at 8 fractions in 2 weeks, histological confirmation of the resected specimen was studied.<sup>4)</sup> At present, a new clinical study with carbon ion radiotherapy alone for T1bN0 is in progress. More cases still have to be enrolled, as this study was just begun in 2008.

### *Uterine Cancer*

The mortality of uterine cancer is following a declining trend, with the treatment results being relatively favorable through the combination of intra-cavitary brachytherapy and external beam radiotherapy. However, for advanced-stage uterine cancer, the treatment results are still unsatisfactory and have so far seen little or no progress, also leading to the

application of chemoradiotherapy. Carbon ion radiotherapy is now being used mainly for locally advanced lesions in an attempt to achieve new breakthroughs in therapeutic results.<sup>36)</sup>

The treatment results of carbon ion radiotherapy for squamous cell carcinoma of the uterine cervix showed serious toxic reactions in the gastrointestinal tract in our early period of clinical studies, with some patients requiring surgical intervention. However, improvements in safety were achieved as a result of more effective irradiation techniques in later clinical studies. When the gastrointestinal tract dose was limited to < 60 GyE, such severe reactions no longer occurred. As dose escalation proceeded, the local control rate also improved. When treatment was with > 62.4 GyE, the local control rate was 69% in patients with stage IVA disease.<sup>37)</sup> Although dose escalation studies are still in progress, carbon ion therapy is considered effective for the treatment of stage III and stage IVa cervical squamous cell carcinoma.<sup>38)</sup>

Treatment of uterine adenocarcinoma has been targeted primarily at non-resectable cervical cancer in a phase I/II dose-escalation study. Although the number of patients with locally advanced adenocarcinoma is small, no patients developed severe acute toxicity and to date most patients remained free of major late complications. Patient enrollment in the trial is still in progress, and the outcomes are pending. However, the early data suggest that carbon ion radiotherapy provides favorable local tumor control and overall survival with acceptable rates of late complications in locally advanced cervical adenocarcinoma.<sup>39)</sup>

## **RARE TUMORS**

### *Non-Squamous Cell Head and Neck Tumors*

Carbon ion radiotherapy was first applied for patients with head and neck tumors in June 1994. In these phase I/II clinical studies, the tumor type consisted of tumors in the nasal cavity, paranasal sinus and other sites, mostly with invasion to the skull base. The patients had locally advanced or post-operative recurrent cancers considered difficult to control with surgery or conventional photon radiotherapy. They were treated using two different dose-escalation schedules: 18 fractions in 6 weeks in the first pilot study and 16 fractions in 4 weeks in the subsequent study. Comparison of toxicities and local tumor control in these two studies revealed that there was no significant difference between the two. In April 1997, the third phase II study was started using a total dose of 57.6 GyE delivering 16 fractions in 4 weeks, which was determined based on the second dose-escalation study. The treatment results showed that a favorable local control rate of as high as 80–90% has been achieved mainly in adenocarcinoma and adenoid cystic carcinoma in the nasal cavity and paranasal sinus.<sup>40,41)</sup>

The three-year local control rate in malignant melanoma

was also > 80%. However, almost half of the patients eventually died from distant metastasis. This result strongly suggests that an increase in survival rates requires a reduction in distant metastasis. For prophylactic therapy against distant metastasis, a new protocol combining carbon ion radiotherapy with chemotherapy was started in April 2001. Carbon ion radiotherapy was administered by a fractionation method of 57.6 GyE/16 fractions/4 weeks combined with concomitant chemotherapy (DAV: day1: dacarbazine (DTIC) 120 mg/m<sup>2</sup> + nimustine (ACU) 70 mg/m<sup>2</sup> + vincristine (VCR) 0.7 mg/m<sup>2</sup>; days 2-5: DTIC 120 mg/m<sup>2</sup>, a total of 5 courses). Some tendency toward improvement in both local control and survival rate in this concurrent and adjuvant chemotherapy has been observed.<sup>42)</sup>

### *Bone and Soft-Tissue Sarcomas*

As bone and soft-tissue sarcomas are generally considered to be photon-resistant and are frequently present close to critical organs, conventional photon radiotherapy is only applied in limited cases. Advanced tumors originating from the para-spinal region, the pelvis and retroperitoneum are not suited for surgical resection in many cases and have poor prognosis. Carbon ion radiotherapy now offers a favorable prospect of improved local control.

Fifty-nine patients were treated in a dose-escalation phase I/II study (total dose ranged from 52.8 GyE to 73.6 GyE in 16 fractions) since June 1996. These patients were not suited to surgical resection or were entirely in-operable. This study produced a favorable tumor control rate of 63%. It was found that especially chordoma and osteosarcoma in the pelvis were prime candidates for carbon ion radiotherapy.<sup>43-45)</sup> For the 10% of those patients with lesions close to the skin surface, it was impossible to avoid high-dose irradiation of the skin. They developed severe reactions such as fibrosis or ulceration of the skin and subcutaneous tissues. However, using irradiation from at least three portals in order to reduce the dose delivered to the skin, such severe reactions no longer occurred. In view of these findings, the recommended dose was fixed at 70.4 GyE in 16 fractions over 4 weeks.<sup>38)</sup> In the following fixed-dose phase II study, 282 patients were enrolled from April 2000. In this study, the 5-year local control rate and 5-year overall survival rate were 81% and 52%, respectively. Overall toxicity was acceptable with 2% skin/soft tissue late G3/4 toxicity.<sup>46)</sup> Carbon ion radiotherapy provided definite local control and offered a survival advantage with acceptable morbidity in bone and soft tissue sarcomas that were hard to cure with other modalities.

### *Choroidal Melanoma*

The incidence of choroidal melanoma in Japan is 20~30 patients a year. This tumor is commonly treated with proton radiotherapy in Western countries. Proton radiotherapy has achieved superior results in terms of both eyeball and vision retention with satisfactory tumor control. There are three

aspects by which carbon ion radiotherapy at NIRS most differs from proton radiotherapy. First, carbon ion therapy is primarily applied to large or extra-large sized tumors that are excluded from proton radiotherapy. Second, we use CT scanning in treatment planning. As a result, the 3-year local control rate of 97.4% was satisfactory and comparable to that reported for proton therapy, and 3-year overall survival rate was 88.2%.<sup>47)</sup> Third, using CT-based planning, irradiation can be performed from two portals to ensure maximum possible prevention of neo-vascular glaucoma after radiation therapy.<sup>48)</sup> At present, this disease qualifies for treatment under HAMT.

### *Lacrimal Gland Cancer*

Malignant epithelial tumors originating in the lacrimal gland also have a low incidence in Japan. Surgery offers poor results because of difficulty in the total tumor eradication. This calls for therapeutic modalities that permit high local control with retention of the eyeball and vision. For this purpose, carbon ion radiotherapy has been employed with a 12 fractions/3 weeks irradiation schedule. So far, 16 patients have been treated, with a total dose of 48 GyE in 5 patients, and 52.8 GyE in 11. It has been shown that determination of the planning target volume including almost the whole orbit is vital to prevent recurrence, even if gross tumor volume is not so large.

## DISCUSSION AND FUTURE DIRECTION

The physical and biological advantage of carbon ion radiotherapy is becoming clear with the two most promising aspects being a high local control rate for many types of radio-resistant tumors and the establishment of a short-course hypofractionated regimen that is effective in local control of various tumors with acceptable morbidity. For several tumors, these high local control rates also can lead to improvement in overall patient survival. In addition, for preventing distant metastasis, carbon ion radiotherapy combined with systemic chemotherapy has been easily initiated without severe side effects in some tumors.

Carbon ion radiotherapy is becoming well-known as the supreme non-invasive local treatment for solid cancer. At present there are a total of seven facilities in operation for charged particle therapy in Japan. These include: NIRS (carbon ions), Tsukuba University (protons); National Cancer Center East: NCCE (protons); Hyogo Ion Beam Medical Center: HIBMC (protons and carbon ions); Wakasa-Wan Energy Research Center (protons); Shizuoka Cancer Center (protons); and Minami-Tohoku Proton Center (protons). Four more facilities are currently under construction in Japan. The three facilities for proton radiotherapy are in Fukui Prefecture, Ibusuki in Kagoshima, and Nagoya city in the middle of Japan, and they will have commercially available accelerators installed. At Gunma University, a new car-

bon facility was completed and began patient treatment in March 2010.

The sole but currently unavoidable disadvantage of particle therapy is the high cost of its technical realization and operation. Large cyclotrons or synchrotrons are needed to accelerate protons and heavier ions to the energy levels required to treat deep-seated tumors. However, developments in physics have permitted facility downsizing, which will decrease the required cost. In fact, the facility at Gumma is about one-third that of HIMAC in terms of size and cost.

From a purely medical point of view, carbon ion radiotherapy was successful for several intractable diseases, such as advanced head and neck cancer, recurrent rectal cancer and inoperable sarcomas. For these diseases, it is clear that there are no comparable results from other modalities, and carbon ion radiotherapy is absolutely necessary to save lives, even though the cost is substantially high. In common cancers, such as lung, liver and prostate cancer, promising results have been also obtained with carbon ion radiotherapy. For these tumor entities, randomized controlled study must be the firmest way of proving the utility of a new modality such as carbon ion radiotherapy. However, it would be very difficult to obtain consent for randomized trials from patients coming to Chiba who would be eager to receive carbon ion radiotherapy. As such, conducting a randomized controlled study to compare other treatment modalities would be highly difficult.

Thus, radiation oncology researchers need to develop new methodologies for the clinical assessment of new health technologies as a complement to a randomized controlled study. Possible future comparative studies of carbon ion radiotherapy may include the following: 1) multi-institutional prospective clinical studies using the same protocols that can be applied to therapies (non-randomized concurrent clinical trials); 2) matched-pair controlled studies in subjects matched to those receiving other therapies; and 3) randomized controlled study between carbon ion and proton or other high-tech radiotherapies.

Currently feasible comparative studies to further clarify the usefulness of carbon ion radiotherapy at various indications include those in which the same protocol applied to other therapies is followed, the backgrounds of subjects are matched, and the treatment desired by the study participants is performed. In this case, consent from study participants can be easily obtained, the study cost is low, and agreement among the participating facilities is relatively easily reached, as the treatment desired by the patients would be provided by the co-operating institutions. For realizing this type of comparative study, a project team has been organized to conduct a multi-institutional prospective prostate cancer study in all particle therapy facilities in operation in Japan. This study is expected to start within 1 or 2 years. This multi-institutional prospective non-randomized concurrent phase

II clinical trial could represent a new methodology for the assessment of new radiotherapy technologies.<sup>49)</sup>

## SUMMARY

The promising aspect of carbon ion radiotherapy for the treatment of cancer lies in its superior biological dose distribution that makes the carbon ion beam the best-balanced particle beam available. Thus, comparison of the ratio of RBE in the peak region against RBE in the plateau region shows that carbon ion beams have the most favorable value of all heavy ion beams.

So far, with the support of the many involved members, considerable evidence has been accumulated in terms of the safety and efficacy of carbon ion radiotherapy for various types of malignant tumors. At the end of 2003, the Institute was successful in obtaining approval for the designation of HAMT by the government, an important landmark for widening the scope of diseases corresponding to carbon ion radiotherapy. The next target will be obtaining approval for this therapy to be included in general practice under the National Health Insurance scheme. Finally, studies aimed at clarifying the greater usefulness of carbon ion radiotherapy and elucidating any advantages from hypofractionation should be considered. A multi-institutional prospective non-randomized concurrent phase II clinical trial is one such new approach, and it will be proposed not only to Japanese, but also to the international community of particle therapy and radiation oncology.

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