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Proceedings of
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27-29 February 2012

King Faisal Specialist Hospital
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NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine

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Organized by

National Institute of Radiological Sciences, Japan

and

King Faisal Specialist Hospital and Research Centre, Saudi Arabia

Aim of the Joint Symposium

Carbon ion therapy to treat radio resistant tumors is presently blooming everywhere around the World with a rising number of projects. Recently USA and China are joining the group of Japanese and European pioneers, Germany and Italy. In that field, Japanese experience with up to 16 years of clinical experience stands as the clinical base for the present development of hydrotherapy worldwide. This joint-symposium summarizes the experiences of carbon ion radiotherapy at the Heavy Ion Medical Accelerator in Chiba (HIMAC) of the National Institute of Radiological Sciences- Japan, where more than 5000 patients were treated with such modality. As well, Saudi Arabia current and future efforts in this field will be presented.

Belal Moftah, KFSHRC
Tadashi Kamada, NIRS

INDEX

Carbon Ion Radiotherapy

Overview of Carbon Ion Radiotherapy

Hirohiko Tsujii

National Institute of Radiological Sciences, Chiba, Japan
Corresponding Author: Hirohiko Tsujii, e-mail address: tsujii@nirs.go.jp

In cancer radiotherapy (RT), ion beams such as proton and carbon ion beams have unique characteristics of improved dose distributions, enabling a delivery of sufficient dose to the target volume while minimizing the dose in the surrounding normal tissues. In addition, carbon ions being heavier than protons provide a higher biological effectiveness with increasing the depth, reaching the maximum at the end of the beam's range (1,2). Over the last decade, carbon ion RT has been applied to a number of tumors that are difficult to control with other modalities, and the number of facilities has been also increased worldwide. In these facilities including National Institute of radiological Sciences (NIRS) in Japan and Gesellschaft für Schwerionenforschung (GSI) in Germany, clinical study has been focused on an attempt to identify tumor sites suitable for carbon ion therapy and to determine the optimal dose-fractionation and irradiation methods (3-8).

1. Expected benefit of carbon ion radiotherapy

Carbon ions are extremely useful in cancer therapy, for even when there are critical organs in the vicinity of the lesion it is possible to safely concentrate sufficient dose in the lesion. Furthermore, as the LET of carbon ions is higher than protons or photons, it has a high RBE in the Bragg peak that is twice or three times greater than that of photons in clinical situation.

Carbon ion beam has further advantageous biological features in that radiation damage to cancer tissue will not easily recover, that the oxygen concentration in the tumor has little effect on radiosensitivity, and that there are only small differences in radiosensitivity among different phases of the cell cycle. Furthermore, comparison of the ratio of the RBE in the peak portion to the RBE in the plateau portion of the different ion beams shows that carbon ion beams have the highest value for this ratio among all particle beams (9,10). This means that carbon ion beams have the best balance of any particle beams in terms of both physical and biological dose distribution.

Such unique features of carbon ions lend themselves to the biological background that the treatment period can be significantly shortened as compared with conventional treatment modalities. Indeed, clinical experiences at NIRS have shown that the hypo-fractionated regimen is effective against a wide range of tumors (3,4,5). For Stage I lung cancer and liver cancer, for example, an ultra-short irradiation schedule capable of being completed in only 1 or 2 sessions has been achieved. Even for those tumors like prostate cancer and head/neck cancer, the fractionation regimens are much shorter than those used in the most sophisticated photon IMRT and proton therapy. This means that the facility can be operated more efficiently, offering treatment for a larger number of patients than is possible with other modalities over the same period of time.

2. Carbon ion therapy facilities

Historically, ion beam radiotherapy was begun using proton beams at the Lawrence Berkeley National

Laboratory (LBNL) in 1954. Since then the efficacy of heavier charged nuclei such as helium, carbon, nitrogen, neon, silicon, and argon had been also assessed for clinical use at LBNL. The major pioneering work for heavy ions was done at LBNL between 1977 and 1992, in which most patients were treated with helium and neon ions. In 1994, the clinical study on C-ion RT was started in NIRS with carbon ions generated by HIMAC that was the world-first accelerator complex dedicated to cancer therapy (Fig1). As of January 2012, there are around 33 operating proton facilities in the world, while carbon ion RT is performed in 5 facilities.

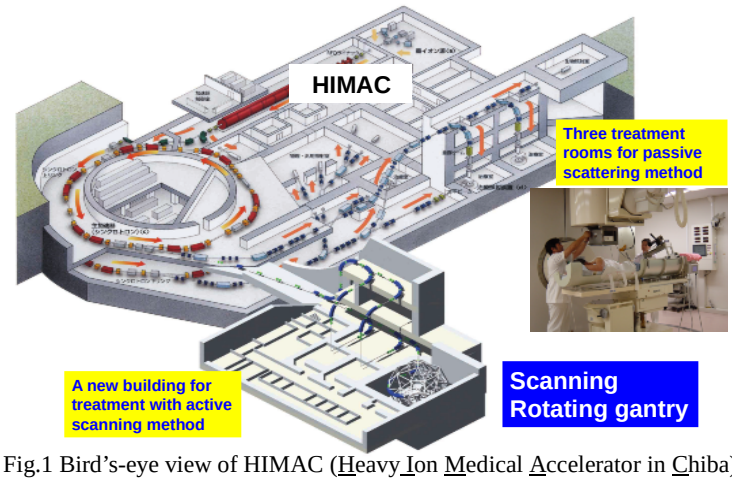

Fig.1 Bird's-eye view of HIMAC (Heavy Ion Medical Accelerator in Chiba)

Following the HIMAC/NIRS, the GSI in Darmstadt started C-ion RT in 1997, which terminated clinical application and was succeeded by Heidelberg Ion-Beam Therapy Center (HIT) in 2009. The HIT is the world's first particle therapy facility for treatment with protons and carbon ions with a scanned beam delivery system. In fact, the Hyogo Ion Beam Medical Center (HIBMC) in Japan, established in 2001, is the first facility dedicated to proton and carbon treatment using a broad beam technique. At the Institute of Modern Physics (IMP) in Lanzhou, China, clinical trials have been performed since 2006, where carbon ion beams with energy up to 100 MeV/u have been supplied for treatment of superficial tumors. Base on technological research and development performed at NIRS, Gunma University in Japan constructed a downsized carbon-ion facility named the Gunma University Heavy Ion Medical Center (GHMC), where clinical study took place in 2010.

In the Foundation CNAO, Italy, the accelerator complex was completed for proton/carbon treatment, in which the clinical study on proton therapy started in October 2011 and C-ion RT is due to start in about one year. Under the license agreement between the GSI and Siemens AG, two facilities modeled on HIT are under construction in Marburg and Kiel in Germany, as well as one in Shanghai, China. At present, however, there is uncertainty whether these institutions will be really built as planned. There are three more institutions that are under construction of carbon ion facility: two in Japan and one in Lanzhow. Among them, the SAGA-HIMAT in Tosu, Japan, is unique in terms that its construction is based on a public-private partnership.

3. Clinical Results of Carbon Ion Radiotherapy

Between 1975 and 1992, a total of 239 patients were treated with a minimum neon physical dose of 10Gy at LBNL. The 5-year disease-specific survival and LC rates suggested that, compared with historical results, neon ion treatment improved the outcome of several types of tumors such as advanced or recurrent macroscopic salivary gland carcinomas, paranasal sinus tumors, advanced soft tissue sarcomas, macroscopic bone sarcomas, locally advanced prostate carcinomas, and biliary tract carcinomas (11,12). Unfortunately, clinical research at LBNL was terminated in 1992 as a result of budget difficulty in addition to the aging of the machine.

Clinical application of heavy ion beams was succeeded by the NIRS in 1994, in which various types of tumors

have bee treated with carbon ions. Between 1994 and 2011, more than 6,000 patients were treated with carbon ions at NIRS (Fig.2, Fig.3), where the benefit of C-ion RT over other modalities has been demonstrated in terms of high LC and survival rates. A significant reduction in overall treatment time with acceptable toxicities has been achieved in most cases. Similar results have been obtained at HIBMC. At GSI, the first patient was treated in 1997 using GSI's heavy-ion synchrotron that had been jointly used for physics research and clinical application. The clinical study at GSI was terminated in 2008, until then they treated a total of 440 patients with carbon ions. Based on these experiences, a new facility named the Ion Therapy Facility (HIT) was built in Heidelberg. At IMP in China, an accelerator that was also primarily built for physics research has been used for C-ion RT. As compared to standard radiotherapy, they prescribed much higher total dose in smaller fractions for superficial lesions, by which they successfully obtained a high LC with relatively low degree of radiation-induced skin reactions.

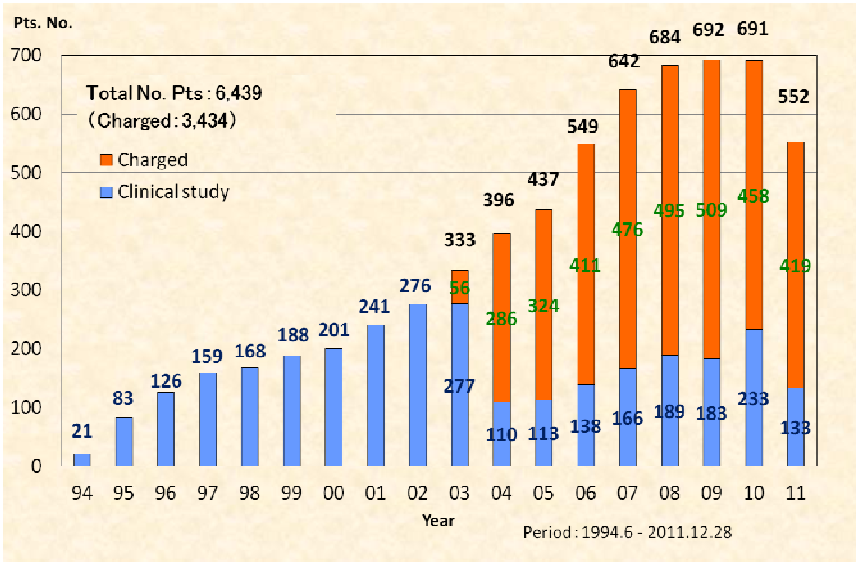

Fig.2 Annual number of patients in carbon ion radiotherapy at NIRS from June 1994 to December 2011

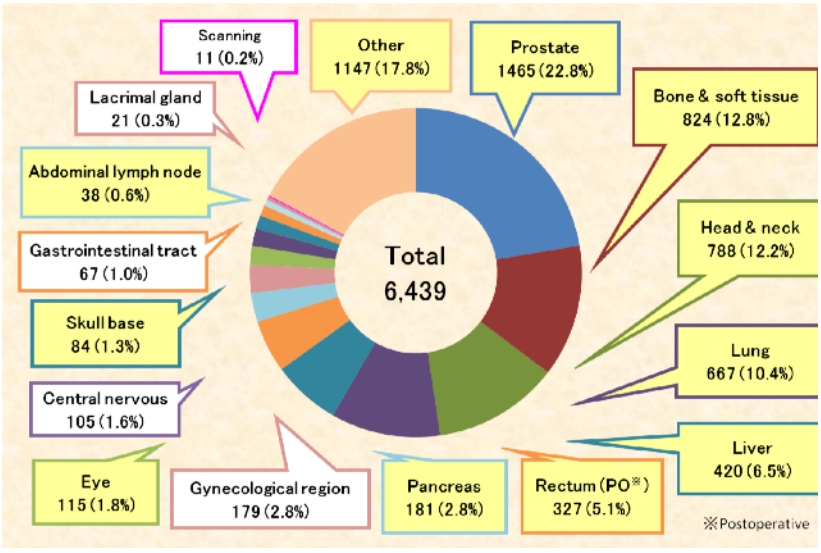

Fig.3 Number of patients enrolled for carbon ion radiotherapy at NIRS from June 1994 to December 2011

Experiences to date indicate that carbon ion RT is advantageous for the following types of tumors.

1) Skull base and para-cervical spine tumor.

2) Advanced non-squamous cell cancer of the head and neck (adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, sarcoma, etc).
3) Non-small cell lung cancer (single fraction RT for Stage I tumor with better result in T2 and locally advanced tumor).
4) Bone and soft tissue sarcoma of the pelvis, paraspinal region, and head/neck.
5) Postoperative pelvic recurrence of rectal cancer.
6) Prostate cancer (short course RT with better result in high-risk group).
7) Hepatocellular cancer (two fraction RT with better result in a large tumor).
8) Uveal melanoma and lacrimal gland tumor (less toxicity by CT-oriented planning)
9) Uterine cervix adenocarcinoma.
10) Pancreas cancer (chemo-carbon RT for locally advanced cancer)
11) Slow growing tumors in any sites.
12) etc

Tumors located in the vicinity of critical organs such as the eye, spinal chord, digestive tract with a relatively large size or irregular shape are good indications for carbon ion RT. However, the tumors that infiltrate or originate in the digestive tract are difficult to control with C-ion RT alone. Regarding dose-fractionations, it has been possible to complete a treatment in significantly short time. Currently, the number of irradiation sessions per patient averages 13 fractions spread over approximately three weeks in carbon ion RT at NIRS. For glioblastoma, however, satisfactory results have not been obtained yet.

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Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas

Reiko Imai, Tadashi Kamada, Hiroshi Tsuji, Katsuya Maruyama, Keiji Matsumoto and Hirohiko Tsujii

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
Corresponding Author: Reiko Imai, e-mail address: r_imai@nirs.go.jp

Abstract

A clinical trial was first initiated in 1996 to evaluate the safety and efficacy of carbon ion radiotherapy for bone and soft tissue sarcomas not suitable for surgery. As of February 2011, a total of 800 patients were enrolled in the clinical trials. Through a dose escalation trial and a subsequent fixed dose trial, it was revealed that carbon ion radiotherapy provided definite local control and offered a survival advantage without unacceptable morbidity for patients with bone and soft tissue cancers that were either difficult or impossible to cure using other modalities.

Introduction

Malignant tumors that originate in the bone and soft tissues (e.g., muscle and adipose tissue) are termed sarcomas, which differ from carcinomas (e.g., lung cancer and stomach cancer). Sarcomas have a much lower incidence than other cancers. In Japan, some 500 and 2000 patients are diagnosed every year with malignant tumors originating from the bone and soft tissue, respectively (1,2). Unlike carcinomas, sarcomas are not lifestyle-related, and they occur at a considerably high rate among young subjects. Sarcomas involve a wide variety of histological types (e.g., osteosarcoma, chondrosarcoma, liposarcoma) and can develop in any part of the body. Depending on the combination of the histological type and the original site of the tumor, the therapeutic approaches vary, and the same treatment can result in different outcomes in different patients depending on these and other factors (3).

Multidisciplinary approaches including surgery, chemotherapy (anti-cancer drugs), and radiotherapy have been most successful for the treatment of bone and soft-tissue tumors in the last 30 years. In particular, the survival rate has been greatly improved for patients with osteosarcomas of the extremity due to progress in chemotherapy (4). In addition, dramatic advances in surgical techniques and prosthetic technology have markedly increased the limb salvage rate. The first-line treatment for bone and soft-tissue tumors is inevitably surgery. However, not all cases are resectable, depending on the tumor site, size, and depth of invasion. The resection of tumors of the extremities is often curative, whereas tumors involving the spine, pelvis, and other axial parts of the body are generally not amenable to surgery, especially advanced cases. Some patients undergoing surgical resection may also run the risk of being deprived of excretory function or suffering a major loss of ambulatory ability (5).

Until recently, unresectable tumors were treated with external radiation therapy and/or brachytherapy combined with chemotherapy. However, chemotherapy was not always effective for the treatment of a wide variety of sarcomas, and conventional radiotherapy achieved good results for only a few types of sarcomas. Therefore, unresectable sarcomas had a very poor prognosis due to the lack of any effective local treatment (6).

Clinical trials of carbon ion radiotherapy for bone and soft tissue sarcomas

Between June 1996 and February 2000, a phase I/II study was carried out to evaluate the efficacy and safety of carbon ion radiotherapy for bone and soft tissue sarcoma (7). This study presented a dose escalation trial using the same fractionation starting from a total dose of 52.8 GyE (3.3GyE per fraction). These patients were not suited for surgical resection. The eligibility criteria for the study are shown in Table 1. Following the trial, a fixed –dose

phase II trial has been ongoing since April 2000 using a total dose of 70.4GyE or 73.6GyE. While the phase II trial included patients with radiation–associated sarcoma, patients with intravascular tumor thrombosis were excluded. A central review of the surgical or biopsy specimens was carried out for all candidates. All patients enrolled in the trials signed an informed consent form approved by the local institutional review board (7-11).

Table 1

Eligibility Criteria
• Histological confirmed bone and soft tissue sarcomas
• Unresectable tumor or the patient declines surgery
• Gross measurable lesion
• Lesion size <15cm in maximum diameter
• KPS 60-100%
• No tumor thrombus
• Signs informed consent form

KPS: Karnofsky Performance Status

Carbon ion radiotherapy for bone and soft tissue sarcomas

The carbon ion beam has higher biological effectiveness and more favorable dose distribution profiles than ordinary radiation beams, like x-ray. The use of the particles provides the target tumor site with a large amount of irradiation possessing a high tumoricidal effect. Three-dimensional treatment planning was performed with the HIPLAN software program (National Institute of Radiological Sciences, Chiba, Japan) specifically designed for planning carbon ion radiotherapy. The standard protocol for the treatment of bone and soft-tissue tumors consists of 16 irradiation sessions delivered over four weeks, once daily four times per week, from Tuesday to Friday Tuesday to Friday. A total dose ranging 52.8 to 73.6 GyE (GyE= carbon physical dose (Gy) x Relative Biological Effectiveness (RBE)) was administered . The fraction dose was modified to be 3.3-4.6GyE. Energies of 350 and 400MeV/n are used mainly for the treatment for axial bone and soft tissue sarcomas, respectively. A margin of 5mm was usually added to the clinical target volume to create the planned target volume. The clinical target volume was covered by at least 90% of the prescribed dose. The patients were usually treated with 3 ports to avoid severe reactions in the normal tissue. One port was used in each session. During the irradiation, the patients lie down in either the supine or prone position with tailor-made immobilization devices on the treatment couch for 20 to 30 minutes in the treatment room. The irradiation with the carbon ion beams lasts for a few minutes.

Results

The phase I/II dose escalation study was carried out on 64 lesions of 57 patients between June 1996 and February 2000 (7). This study produced a favorable tumor control rate of 89% at 1 year, and 63% at 3 years and 5 years, respectively. The overall survival rates were 82% at 1 year, 47% at 3 years, and 37% at 5 years, respectively. The median survival was 31 months. There was a significant difference in the results for the local control rate achieved with a total dose of 57.6GyE or less and that with 64.0GyE or more. As
7 of the 17 patients treated with 73.6GyE were found to have Grade 3 RTOG acute reactions in the skin, the dose escalation was halted at this dose level. These findings made it clear that with a dose fractionation regimen of 16 fractions over 4 weeks, a total dose of 70.4GyE was the maximum applicable dose in patients for whom there was sufficient skin close to the tumor, while a total dose of 73.6GyE was possible in other cases. When we started

using at least three portals in order to reduce the dose delivered to the skin, such severe reactions were no longer observed. In view of these findings, the recommended dose for axial bone and soft tissue sarcomas was fixed at 70.4 GyE in 16 fractions over 4 weeks.

In the subsequent fixed-dose phase II study started in April 2000, 500 have been enrolled as of February 2011. The clinical characteristics of this study are summarized in Table 2.

Table 2
The patient characteristics of the phase II study

Characteristics		No (N=495 pts)
Age		
Median		58 (11-87)
Sex		
Male:Female		288:207
Tumor sites		(N=514 lesions)
Pelvis		388
Spine/para-spine		96
Extrimities/others		30
Histology		
Bone		405
	Chordoma	177
	Chondrosarcoma	81
	Osteosarcoma	81
	Ewing/ PNET	28
	Others	38
Soft Tissue		109
	MFH	21
	MPNST	15
	Synovial sarcoma	11
	Leiomyosarcoma	11
	Others	51

The number of patients analyzed for six months or longer after the treatment included 514 lesions of 495 patients. The total a dose of 73.6GyE (4.6GyE /fraction) was applied for 10 patients, 64.0GyE (4.0GyE /fractions) for 32 patients and 67.2GyE (4.2GyE/fractions) for 70 patients. The remaining 376 patients were treated with a dose of 70.4GyE (4.4gyE/fraction). As of August 2011, the 2-year and 5-year local control rates were 85% and 69%, respectively. The two–year and 5-year overall survival rates were 79% and 59%, respectively (Fig 1). The types of radiation-related toxicity are summarized in Table 3. Overall, the toxicity was acceptable, with 2% skin/soft tissue late G3/4 toxicity observed. Late skin toxicities including, grade 3 in 6 patients and 4 in 1 patient were also observed. These late skin reactions suggest that there are other risk factors, in addition to the total dose. These are thought to include the following: 1) subcutaneous tumor invasion, 2) a large tumor volume, 3)

sacrococcygeal involvement, 4) previous surgery, 5) additional chemotherapy and 6) irradiation using 2 portals. It was possible to prevent the skin reactions by irradiation using over 3 portals in order to reduce the dose administered to the skin surface (12). The incidence of Grade 3 or higher late akin reactions in the patients receiving a total dose of 70.4GyE with over 3 portals has been within the acceptable level for the past several years.

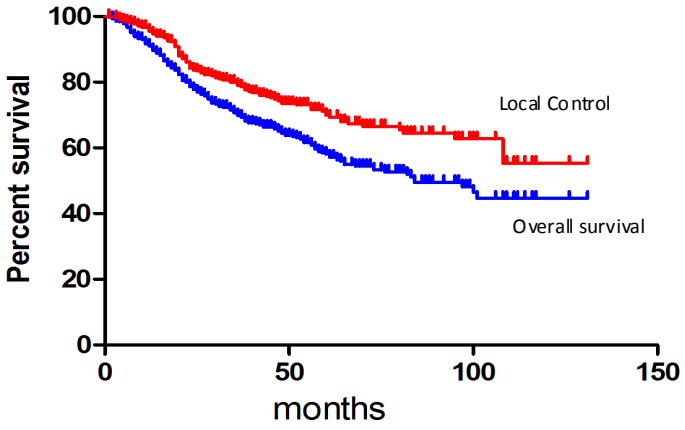

Figure1. Actual local control and overall survival rate in the 495 patients with bone and soft tissue sarcomas enrolled to phase II study. The 5-year local control rates was 69% and the 5-year overall survival rates was 59%.

Table 3

Late radiation morbidities in the phase II study

		Grade					
	No	0	1	2	3	4	5
Skin	506	4	475	20	6	1	0
GI tract	439	437	2	0	0	0	0
Spinal Cord	46	45	0	1	0	0	0

Among the bone and soft-tissue sarcomas treated with carbon ion radiotherapy at our hospital, sacral chordomas accounted for the largest proportion. Sacral chordoma is a rare tumor. Surgery is the first-choice of treatment, but it is not always possible. Since sacral chordomas usually develop gradually, they are often left undetected until they start to cause pain and other symptoms. A lot of patients referred to our hospital presented with a sacral chordoma over 10 cm in diameter. The sacrum houses the sacral nerves, which innervate the excretory functions and ambulation. Depending on the level of the tumor involvement to the sacral bone, excision of these nerves causes permanent gait, excretory and other disabilities, and it impairs the patients' quality of life. Therefore, curative surgery for sacral chordoma (sacrectomy) is one of the most invasive surgeries. Sacral

chordomas frequently occur among the elderly population, who are also often contraindicated for surgery because of either comorbid diseases or overall frailty. Ninety-five patients with sacral chordoma received carbon ion radiotherapy between 1996 and 2007(8). The median age of the 95 patients was 66 years. Eighty–four patients had not been treated previously, while the other 11 patients had a locally recurrent tumor following a previous resection. The median tumor diameter was 9 cm. The carbon ion dose ranged from 52.8GyE to 73.6G. The 5-year local control rate was 88%, and the median time to local failure was 35 months (13-60 months). The 5 year overall survival rate was 86%, with a median follow-up of 42 month (13-112 months) (Fig2). Of the 95 patients, 91% remained ambulatory with or without a supportive device. Two patients experienced severe skin or soft tissue reactions requiring a skin graft. Fifteen patients experienced severe sciatic nerve complications requiring continuing medication, and had impairment of their ordinary life. As of February 2011, 183 chordomas of various types were treated with carbon ion radiotherapy.

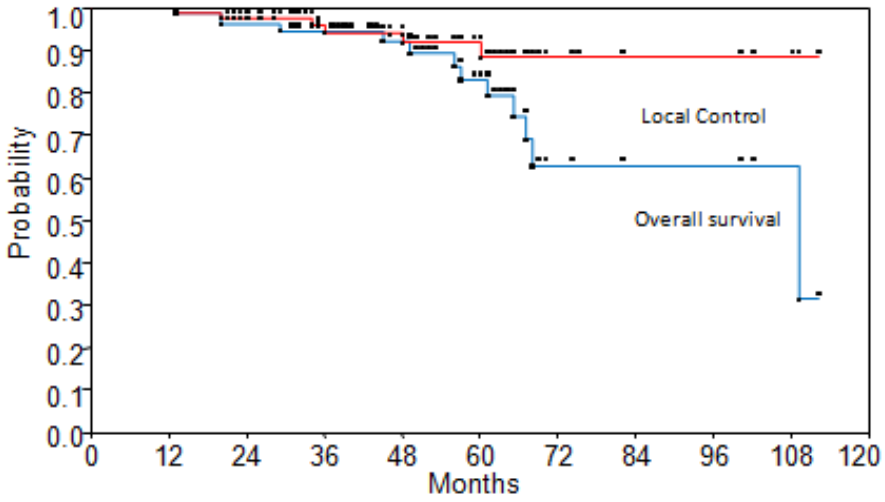

Figure2. Actual local control and overall survival rate in the 95patietns with sacral chordoma. The 5-year local control rate was 88% and the 5 year overall survival rate was 86%.

Osteosaromas of the trunk constituted the next largest group. For the treatment of osteosarcomas of the extremity, which develop with a high incidence among youth, the paradigm based on a combination of surgery and chemotherapy has been well-established, and carbon ion radiotherapy is unlikely to outweigh their advantages. The 5-year local control and 5-year overall survival rates for the 78 patients with unresectable osteosarcoma of the trunk were 61% and 32%, respectively (Fig3). The median diameter of the tumors was 9 cm. As reported in the literature, in the cases of unresectable osteosarcoma, the survival rate was 10% or less. Therefore, carbon ion radiotherapy appears to provide a survival benefit. The tumor size was one of the most important prognostic factors in surgery cases. In patients with unresectable osteosarcoma of the trunk who received carbon ion radiotherapy, the tumor volume was a prognostic factor for the survival and local control rate as well. Thirty-eight patients with a tumor volume of less than 500cc showed a 5-year local control rate of 87%, while forty patients with a volume of more than 500cc had a rate of 21%. The five-year survival rate of the 38 patients with smaller tumors was 46%, while that of the larger tumor group was 19%.

Chondrosarcoma is the second most common primary malignant bone tumor. Surgery has been considered the main form of treatment for chondrosarcoma, and the definitive en bloc resection of the tumor is mandatory to obtain long term disease free survival. However, radical surgical intervention for chondrosarcoma of the trunk has sometimes been associated with substantial morbidities. From 1996 to 2009, 71 patients with chondrosarcoma received carbon ion radiotherapy. The clinical target volumes ranged between 25 and 2900 cm3 (median 488

cm3). At 5 years, the actuarial overall local control rate and overall survival rate were 60% and 60%, respectively (Fig4). Four patients experienced grade 3 and/or 4 skin/soft tissue late reactions in this series.

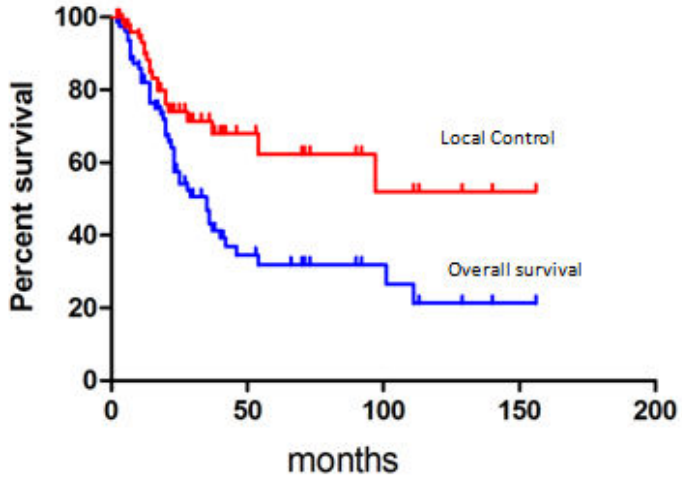

Figure3. Actual local control and overall survival rate in the 78 patients with osteosarcoma of the trunk.The 5-year local control and 5-year overall survival rates were 61% and 32%, respectively.

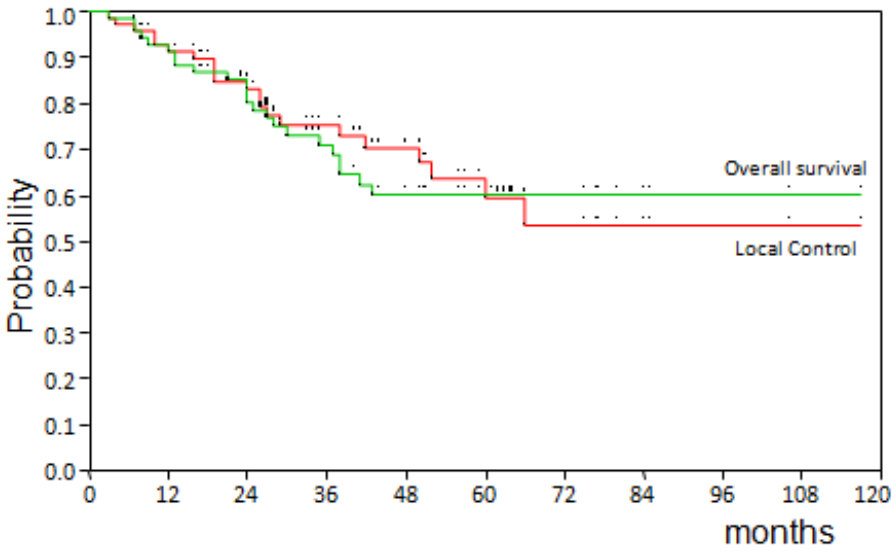

Figure4. Actual local control and overall survival rate in the 71patietns with chondrosarcoma. The 5-year local control rate was 60% and the 5 year overall survival rate was 60%.

Table 4

The result for carbon ion radiotherapy for sacral chordoma

	No of pts	Treatment	5y-LC	5y-OS	10y-OS
MGH(13)	27	Surgery+proton	72%	82%	62%
LBL(14)	14	Surgery+He-ion	55	85	22
Mayo(15)	52	Surgery	56	74	52
NIRS(8)	95	C-ion	88	86	

LC: local control, OS: overall survival

Discussion

In this study, carbon ion radiotherapy was well tolerated and demonstrated substantial activity against sarcomas. These results were obtained in patients with advanced and/or chemo-resistant gross lesions not suited for surgical resection, and were located mainly in the trunk. The results of carbon ion radiotherapy using a total dose of 64GyE to 73.4GyE in 16 fractions over four weeks were satisfactory, considering the candidates were disqualified from surgery. However, it is imperative to continue with long term follow-up to assess the safety and efficacy of carbon ion radiotherapy. With the development of the current research, the possibility of a shorter fractionation regimen should also be explored. The use of a hypofractionated regimen would allow the facility to operate more efficiently and to offer treatment for a larger number of patients. The indications should be expand to not only unresectable cases, but also elderly patients and patients with major functional loss subsequent to surgical resection. While previous experience with carbon ion radiotherapy to the extremities has so far been observed for patients intractable to limb-salvage surgery, widening the scope to limb-retaining therapy should thus be considered.

Conclusion

Carbon ion radiotherapy is an effective local treatment for patients with bone and soft tissue sarcomas for whom surgical resection is not a viable option, and it shows great promise as an alternative to surgery. The morbidity rate of carbon ion radiotherapy has so far been acceptable although the long-term safety of this approach for patients with sarcomas will need to be monitored.

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Carbon Ion Radiotherapy for Malignant Head-and-Neck Tumors

Azusa Hasegawa, Masashi Koto, Ryo Takagi, Akira Fujikawa, Takamichi Morikawa,
Tadashi Kamada, and Hirohiko Tsujii

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan.
E-mail: azusa@nirs.go.jp,

Abstract

To evaluate the efficacy of carbon ion radiotherapy for malignant head-and-neck tumors.
Between April 1997 and February 2011, 407 cases with locally advanced, histologically proven, and primary or recurrent malignant tumors of the head-and-neck were treated with carbon ions. Treatment dose was 64.0 GyE in 16 fractions over 4 weeks (or 57.6 GyE when a wide area of skin was included in the target volume).
There were no acute reactions worse than grade 3 and no late toxicities worse than grade 2. The five-year local control and overall survival rates were 73% and 53%, respectively. But the five-year local control rate was 24% for bone and soft tissue sarcomas, and the five-year overall survival rate was 35% for malignant melanomas.
Carbon ion radiotherapy for malignant head-and-neck tumors can be described as presenting no clinical problems. Although local control of carbon ion radiotherapy was promising for malignant head-and-neck tumor excluding sarcoma, the survival rate was not commensurate with the favorable local control rate of malignant melanoma. On the basis of the results of the analysis, this part of the study was divided into two additional protocols, one for bone and soft tissue sarcomas and another for mucosal malignant melanomas.

1. Phase II Clinical Trial for Malignant Head-and-Neck Tumors (Protocol 9602)

Introduction

A clinical trial of carbon ion radiotherapy for malignant head-and-neck tumors was conducted under the "Phase I/II Clinical Trial (Protocol 9301) on Heavy Particle Radiotherapy for Malignant Head-and-Neck Tumors", that was initiated in June 1994 by way of a dose escalation study using18 fractions over 6 weeks. This trial was followed by another dose escalation study that commenced in April 1996 under the title of "the Phase I/II Clinical Trial (Protocol 9504) on Heavy Particle Radiotherapy for Malignant Head-and-Neck Tumors" using 16 fractions over 4 weeks. Based on the outcome of these two studies [1], the "Phase II Clinical Trial on Heavy Particle Radiotherapy for Malignant Head-and-Neck Tumors (Protocol 9602)" was initiated using 64.0GyE in16 fractions over 4 weeks (or 57.6 GyE in16 fractions over 4 weeks when a wide area of skin was included in the target volume) in April 1997 (Fig. 1).

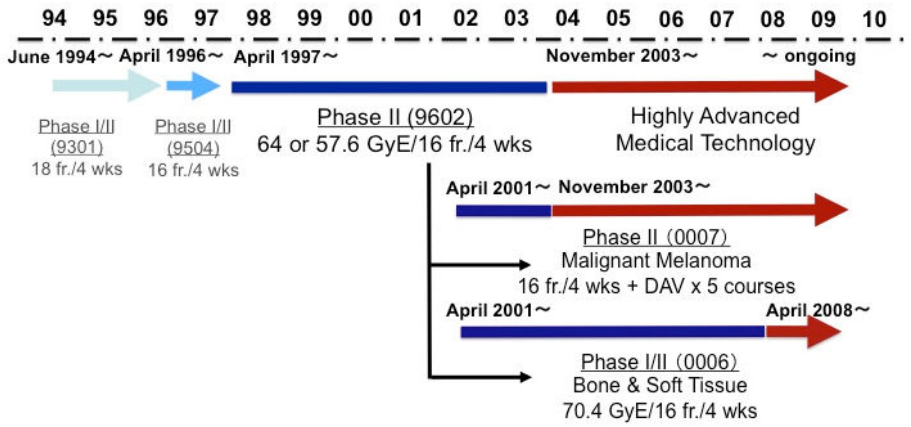

Figure 1. Carbon Ion Radiotherapy for Malignant Head-and-Neck Tumors

Patients and Methods

The eligibility criteria for enrollment in this phase II study were the presence of histologically proven malignancy, a measurable tumor in the head-and-neck region including N0M0 in principle, with no co-existent malignant active tumor, no distant metastasis to other parts, an age range from 15 to 80 years and a prospective prognosis of at least 6 months or longer. The candidates were also required to have a Karnofsky performance status index (KPS) of 60% or more and to give their written informed consent for inclusion in this clinical study. A further requirement was the absence of prior radiotherapy for the carbon-ion treated area, the absence of intractable inflammatory lesion and an interval of at least four weeks from completion of the last chemotherapy.

The phase II study commenced in April 1997, and by February 2011 a total of 409 patients with 412 lesions was registered (three patients had secondary lesions after the initial treatment). Five of the 409 patients were excluded from the analysis because of 1) carbon ion radiotherapy had to be cancelled for two patients with malignant melanoma due to a deterioration of their symptoms, 2) one patient with lacrimal gland tumor was diagnosed as a metastasis from the thyroid gland before carbon ion radiotherapy, 3) the ameloblastoma patient was diagnosed as a benign tumor after histological re-examination and 4) the histological confirmation was done by cytology only. The data for 407 lesions of 404 patients treated until February 2011 are recorded as follows: Patient age range was from 16 to 80, with a median of 58 years, with 192 males and 212 females. Histologically, the tumors were classified as follows: 151 with adenoid cystic carcinoma, 102 with malignant melanoma, 50 with adenocarcinoma, 25 with squamous cell carcinoma, 15 with mucoepidermoid carcinoma, 13 with papillary adenocarcinoma, 7 with acinic cell carcinoma, 7 with undifferentiated carcinoma, 6 with osteosarcoma and 31 with other histological types. There were six cases of T1, 34 of T2, 63 of T3, 174 of T4, 92 of post operative, 27 of post chemotherapy, 9 of post operative and post chemotherapy and one of post carbon ion radiotherapy. Carbon ion radiotherapy was administered using 16 fractions over 4 weeks. The 407 lesions were irradiated with a dose of 57.6GyE in 265 cases and with 64.0GyE in 142 cases.

Results

Acute reactions were of a minor nature, as 16 patients (4%) showed a grade 3 skin reaction, 68 patients (17%) showed a grade 3 mucosal reaction. Late toxic reactions comprised of a grade 2 skin reaction in 8 patients (2%) and mucosal reactions in 14 patients (4%), with no evidence of radiation-induced toxicities worse

than these. This therapy can therefore be described as presenting no clinical problems.

The local tumor reactions within six months consisted of CR for 51 patients, PR for 190 patients, NC for 162 patients, and PD for 5 patients. The response rate was 59%. The five-year LC and OS rates were 73% and 53%, respectively. The five-year LC rate according to histological type was 77% for the 50 adenocarcinomas, 74% for the 151 adenoid cystic carcinomas, 79% for the 102 malignant melanomas, 77% for the 25 squamous cell carcinomas and 24% for the 14 bone and soft tissue sarcomas. The five-year OS rate was 62% for adenocarcinomas, 72% for adenoid cystic carcinomas, 35% for malignant melanomas.

Discussion

The overall LC rate was 73% at 5 years. The therapeutic effectiveness was particularly outstanding for adenoid cystic carcinoma, a tumor type that is intractable to photon radiotherapy. Treatment results of surgery with or without radiotherapy ranged from 56% to 93% for the five-year LC rate and from 57 to 77% for the five-year survival rate [2-5] (Table 1). In the present study, the five-year LC rate was 74%, in spite of including 78 cases (52%) of T4 and 40 cases (26%) that had recurrent tumors after surgery and/or chemotherapy.

Table1. Clinical characteristics of reported cases of adenoid cystic carcinoma

Institutions	N		5-year local control rate (%)	5-year survival rate (%)
Florida [2]	101	Radiotherapy alone	56	57
		Radiotherapy + Surgery	91	77
MGH [3]	23	Proton +/- Surgery	93	77
Washington [4]	151	Neutron	57	77
Heidelberg [5]	29	Neutron +/- Surgery	75	59
NIRS	151	Carbon	74	72

Although the local control of carbon ion radiotherapy was promising for malignant head-and-neck tumor excluding sarcoma, the survival rate was not commensurate with the favorable local control rate of the malignant melanoma. Based on the results of preliminary analysis of this protocol (Protocol 9602), two protocol were derived with effect from April 2001 into 1) the “Phase I/II Clinical Trial of Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas in Head-and-Neck (Protocol 0006)” designed as a dose escalation study for bone and soft tissue tumors, and 2) the “Phase II Clinical Trial of Carbon Ion Radiotherapy Combined with Chemotherapy for Mucosal Malignant Melanoma in Head and Neck (Protocol 0007)” for the treatment of malignant melanoma with concomitant chemotherapy.

2. Phase I/II and II Clinical Trials for Bone and Soft Tissue Sarcomas in Adult Head-and-Neck (Protocol 0006)

Introduction

Phase I/II protocol was commenced in April 2001 for the purpose of a dose escalation study against bone and soft tissue sarcomas in the head-and-neck, since the preliminary analysis of the phase II clinical trial for malignant head-and-neck tumors (Protocol 9602) suggested that the local control and survival of bone and soft tissue sarcomas in the head-and-neck was clearly worse than other malignant tumors. We adopted 70.4 GyE in

16 fractions over 4 weeks as an initial prescribed dose in the present study. According to following toxicities, we might be able to proceed to the next irradiation dose; however, in the present study, because the local control rate had been approximately 100% with the initial dose for the period of the present study and because it was definitive that more than 70.4 GyE would make many unacceptable adverse effects from the results of carbon ion dose escalation study for sarcomas in the trunk in our institution, Kamada et al. described that 4 of 17 patients had grade3 late toxicities in the trunk with more than 70.4 GyE [6], we determined that 70.4 GyE is a recommend irradiation-dose for unresectable bone and soft tissue sarcomas in adult head-and-neck. This phase I/II study was completed on February 2008. From April 2008, phase II clinical study was started with same dose fractionation.

Patients and Methods

The 41 patients included in the analysis between April 2001 and February 2011 consisted of 20 males and 21 females. Two of the 41 patients were excluded from this analysis because of 1) one female patient had past history of whole body irradiation for her acute lymphocytic leukemia, 2) another female patient with MFH was diagnosed as a benign tumor after histological re-examination. The age range of the 39 patients was from 17 to 78, with a median of 48 years. They consisted of 12 patients with osteosarcoma, 5 with MFH, 3 with chondrosarcoma, 3 with hemangiopericytoma, 3 with spindle cell sarcoma, 2 with myxofibrosarcoma, 2 with leimyosarcoma, 2 with small round cell sarcoma, and 7 with other histological types.

Results

In preliminary analysis of the 39 patients who had follow-up period for more than six months, almost of all patients presented less than grade 2 acute reactions; however, five patients presented a grade 3 mucosal reaction. All late skin and mucosal reactions were grade 1 or less. The local tumor reactions within six months consisted of CR for 3 patients, PR for 11 patients, SD for 25 patients, and PD for no patients. The response rate was 36%. The five-year LC and OS rates were 73% and 48%, respectively (Fig. 2).

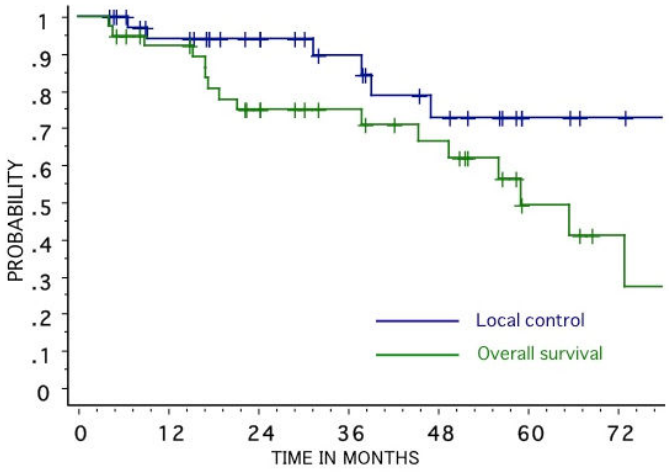

Figure 2. Local Control and Overall Survival of Bone and Soft Tissue Sarcomas

Discussion

Bone and soft tissue sarcomas in the head-and-neck are rare mesenchymal malignant neoplasms accounting for less than 10% of all bone and soft tissue sarcomas and approximately 1% of all head-and-neck neoplasms. Willers et al. said that wide resection margins are anatomically difficult to achieve, and the delivery of high radiation dose can be limited by the vicinity of critical normal tissue structures (spinal cord, brain stem, optic chiasm, eyes). Accordingly, the local control rates for head-and-neck sarcomas are lower compared to the extremities [7]. The five-year LC rate of combined surgery and radiotherapy is 60-70%. The LC of surgery alone is around 54% and that of radiotherapy alone is 43- 50% [8]. However, in unresectable sarcomas, the LC and survival prognosis were miserable. Conventional radiotherapy with a total dose less than 65 Gy showed no local control [9-11].

Results of carbon ion radiotherapy in our previous study (9602) for bone and soft tissue sarcomas in the head and neck, in which study patients were treated using 64.0 or 57.6 GyE in 16 fractions, showed 24% of the five-year LC rate. On the other hand, the five-year LC rate of this study (0006) was 73%. This result showed improved tendency compared with surgery with or without radiotherapy.

3. Phase II Clinical Trial for Mucosal Malignant Melanoma in Head-and-Neck Combined with Chemotherapy (Protocol 0007)

Introduction

Although the phase II clinical study for malignant head-and-neck tumors (Protocol 9602) had achieved a satisfactory local control rate for mucosal malignant melanomas, the survival rate was not commensurate with the favorable local control rate of malignant melanomas. In view of this result, this protocol was started in April 2001 for the purpose of prophylactic therapy against distant metastasis, the major cause of death in malignant melanoma of the head-and-neck region.

Patients and Methods

Carbon ion dose was 57.6 GyE in 16 fractions over 4 weeks. Concomitant chemotherapy (DAV: Day 1: DTIC 120mg/m2 + ACU 70mg/m2 + VCR 0.7mg/m2; Days 2~5: DTIC 120mg/m2, 4 weeks' interval, a total of 5 courses) was administered at two courses before, and three courses after carbon ion radiotherapy. The results for the seven patients treated until February 2002 show that at the time of completion of the two courses of DAV chemotherapy prior to carbon ion radiotherapy, there were PR for 2 patients, NC for 2 patients and PD for 3 patients, necessitating the early commencement of carbon ion radiotherapy. From April 2002, carbon ion radiotherapy and DAV chemotherapy were carried out concurrently.

The 103 patients included in the analysis between April 2001 and February 2011 consisted of 47 males and 56 females. Their age ranged from 26 to 79 years, a median of 62 years. Their KPS ranged from 70% to 100%, with a median of 90%. As for the tumor site studied, there were 82 nasal cavity and paranasal sinus, 13 oral cavity, 5 pharynx and 3 orbit.

Results

The acute reactions of 103 patients who have a follow-up time more than 6 months were consisted of one patient with a grade 3 skin reaction and 21 patients (20%) with a grade 3 mucosal reaction while the other toxicities that were observed were grade 2 or less. All late reactions in both the skin and mucosa were grade 1

or less.

The local tumor reactions within six months consisted of CR for 22 patients, PR for 47 patients, SD for 35 patients, and PD for no patients. The effective rate was 66%. The five-year LC and OS rates of all patients were 79% and 55%. In 96 concomitant patients, the five-year LC and OS rates were 81% and 58%, respectively.

Discussion

The reported local failure of systemic therapy including surgery, radiotherapy and chemotherapy is very high (45-54%) [12,13]. The five-year LC rate of carbon ion radiotherapy showed 79% in this protocol. These results will show an effectiveness of carbon ion radiotherapy for the local control of mucosal malignant melanoma in the head-and-neck. The review articles [14-20] reported the five-year survival rates of 17-35% (Table 2), which is attributed mainly to distant metastasis. The five-year OS rate of carbon ion radiotherapy showed 37% in 9602 and 55% in 0007 protocol. There will be some tendency of improving result in concomitant and adjuvant chemotherapy (Protocol 0007) (Fig. 3).

Table2. Clinical characteristics of reported cases of mucosal malignant melanoma

	Authors	N	5-year OS (%)
Radiotherapy	Gilligan [14]	28	18
(+/- Surgery)	Shibuya [15]	28	25
Surgery	Chang [16]	163	32
(+/- RT, +/- Chemo)	Shah [17]	74	22
	Patel [18]	59	35
	Lund [19]	58	28
	Chaudhry [20]	41	17
Carbon ion alone	NIRS	102	37
Carbon ion + Chemo	NIRS	89	58

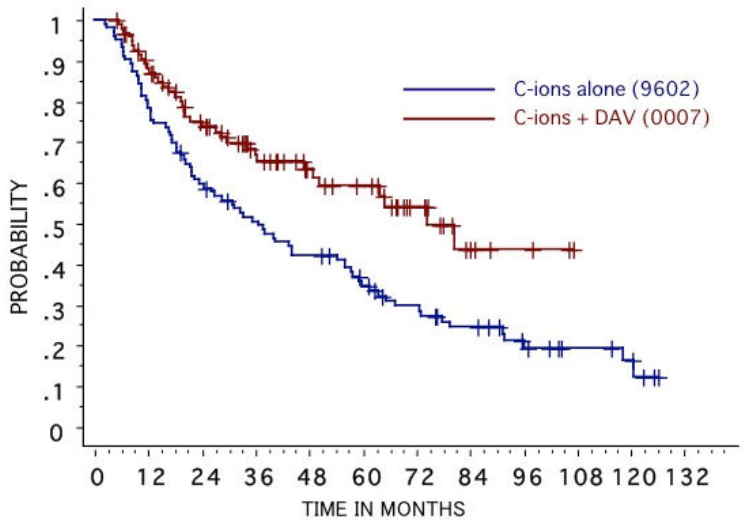

Figure 3. Overall Survival of Mucosal Malignant Melanomas

Conclusion

Malignant head-and-neck tumors are therapeutically very diverse because of the many important organs present in this region and the great variety of tissue types. Carbon ion radiotherapy also requires considerable versatility in terms of the use of a specific radiation dose suited for the particular histological type and the application of concurrent chemotherapy. At present, efforts are being made to increase the patient numbers in order to produce results that can provide cogent clinical evidence.

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Carbon Ion Radiotherapy for Skull Base and Paracervical Tumors

Masashi Koto, Azusa Hasegawa, Ryo Takagi, Akira Fujikawa, Takamichi Morikawa, Hirohiko Tsujii, and Tadashi Kamada

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan.
E-mail: koto@nirs.go.jp

Abstract

Purpose: To estimate the toxicity and efficacy of carbon ion radiotherapy for skull base and paracervical tumors in clinical trials.

Patients and Methods: A phase I/II dose escalation study for skull base and paracervical tumors was initiated in April 1997. The patients were treated with 16 fractions for 4 weeks with a total dose of 48.0, 52.8, 57.6, or 60.8Gy equivalents (GyE). In April of 2004, a phase II study was initiated with an irradiation schedule of 60.8GyE in 16 fractions over four weeks. There were 76 patients included in the analysis. Histologically, 44 patients had chordoma, 12 chondrosarcoma, 9 olfactory neuroblastoma, 7 malignant meningioma, 1 giant cell tumor, and 1 had a neuroendocrine carcinoma. The patients were treated with a dose of 48.0 GyE (4 patients), 52.8 GyE (6 patients), 57.6 GyE (9 patients) or 60.8 GyE (57 patients).

Results: The follow-up periods ranged from 3 to 158 months, with a median period of 46 months. At the time of the analysis, there was no evidence of any serious acute (Grade ≥4) or late (Grade ≥3) reactions. The 5-year local control and overall survival rates for all patients were 88% and 82%, respectively. The 5-year local control and overall survival rates for chordoma patients were 88% and 87%, respectively.

Conclusion: A carbon ion dose of 60.8GyE in 16 fractions was effective and safe for the treatment of skull base and paracervical tumors.

Introduction

The limiting factor for photon radiotherapy conventionally applied to skull base and paracervical tumors is the adjacent normal tissue, leading to poor local control by photon radiotherapy. On the other hand, proton radiotherapy with its superior physical-spatial distribution has provided a major improvement in local control with regard to the possibility of dose escalation. It has been pointed out, however, that in certain patient groups, it is difficult to achieve local control with proton radiotherapy, even at elevated doses. It has thus been recognized that 1) chordoma patients have a worse prognosis than chondrosarcoma patients, 2) among the chordoma patients, the prognosis for paracervical chordoma patients is worse than for patients with skull base chordomas, and it is worse for females than for males. Therefore, the high LET of carbon ion radiotherapy has promising potential for treatment of these intractable skull base and paracervical tumors.

Patients and Methods

1. Protocol

A phase I/II clinical trial using a schedule of 16 fractions over 4 weeks was initiated in April 1997. Chordoma, chondrosarcoma, meningioma, and other tumors arising from the skull base or paracervical spine located

superior to the C2 vertebra were targeted. Only patients with residual tumors after surgery or with inoperable tumors were permitted to enroll in the carbon ion radiotherapy study. The eligibility criteria for enrollment in this clinical trial were the presence of a histologically proven tumor, patient age ranging from 15 to 80 years, a KPS of 60% or more, neurological function of grade I or II, the absence of anti-cancer chemotherapy within the previous four weeks, asurvival expectancy of six months or more, and no distant metastasis.

2. Treatment planning

A set of 2.5-mm-thick CT images was taken for treatment planning, with the patient placed in a custom-made immobilization device with a dental mouthpiece. The metals in the oral cavity were removed before the treatment planning CT to avoid artifacts on CT images including the tumor. The gross tumor volume (GTV) was delineated on the CT images using CT-MRI fusion. The clinical target volume was defined with an adequate safety margin for the GTV. A margin of 5 mm was usually added to the CTV to create the planning target volume. In case where the tumor was close to critical organs, such as the brain stem or spinal cord, the CTV margin was reduced to spare these organs. Three-dimensional treatment planning was performed with the HIPLAN software program (National Institute of Radiologic Sciences, Chiba, Japan) designed for carbon ion therapy. Carbon ion radiotherapy was given once daily, 4 days a week. The patients were treated with two to five ports. One port was used in each treatment session. At every treatment session, the patient's position was verified with a computer-aided on-line positioning system. The patient was positioned on a treatment couch with the immobilization devices, and digital orthogonal X-ray TV images in that position were taken and transferred to the positioning computer. They were compared with the reference image on the computer screen and the differences were measured. The treatment couch was then moved to the matching position until the largest deviation from the field edge and iso-center position was less than 2 mm.

3. Patients

The carbon ion dose was escalated in successive stages: 48 GyE in 4 patients, 52.8GyE in 6 patients, 57.6GyE in 9 patients and 60.8GyE in 9 patients. The phase I/II clinical trial was concluded in February 2004, and in April 2004, a phase II clinical trial was initiated under the Highly Advanced Medical Technology scheme, with an irradiation schedule of 60.8 GyE in 16 fractions over 4 weeks. Forty-eight patients were enrolled in this trial until February 2011.The 76 patients included in the analysis consisted of 32 males and 44 females. Their ages ranged from 16 to 78 years, with a median of 50 years. Histologically, 44 patients had chordoma, 12 chondrosarcoma, 9 olfactory neuroblastoma, 7 malignant meningioma, 1 giant cell tumor, and 1 had neuroendocrine carcinoma. Sixty-one tumors were located in the skull base region and 15 in the paracervical region.

4. Statistical analysis

Acute toxicity was assessed based on the Radiation Therapy Oncology Group (RTOG) score, and late toxicity was determined based on the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) score. Local control and overall survival rates were calculated according to the Kaplan-Meier method.

Results

1. Toxicity

The follow-up periods ranged from 3 to 158 months, with a median period of 46 months. Acute reactions were of a minor nature, as one of the patients in the 48 GyE group showed a grade 3 skin reaction, and one patient in the 57.6GyE group and 3 patients in the 60.8 GyE group developed a grade 3 mucosal reaction. A late grade 2

brain reaction was detected in one of the patients in the 57.6 GyE group and 2 patients in the 60.8GyE group, but no other adverse reactions were observed. At the time of analysis, there was no evidence of any serious acute (≥ Grade4) or late (≥Grade3) reactions.

2. Local Control and Survival

The effect on the tumor was primarily stable disease within six months after carbon ion radiotherapy, and there were no significant changes in tumor size in most cases during the follow-up periods. Local control was defined as showing no evidence of tumor regrowth by MRI, CT, physical examination, or biopsy. The 5-year local control and overall survival rates for all patients were 88% and 82%, respectively (Fig. 1). The 5-year local control rate according to histological types was 88% for the 44 chordomas, 86% for the 12 chondrosarcomas, 100% for the 9 olfactory neuroblastomas, and 80% for the malignant meningiomas. The five-year overall survival rate was 87% for patients with chordomas, 63% for chondrosarcomas, 56% for olfactory neuroblastomas, and 69% for malignant meningiomas. The 5-year local control and overall survival rates for the patients treated with a dose of 60.8 GyE were 91% and 77%, respectively.

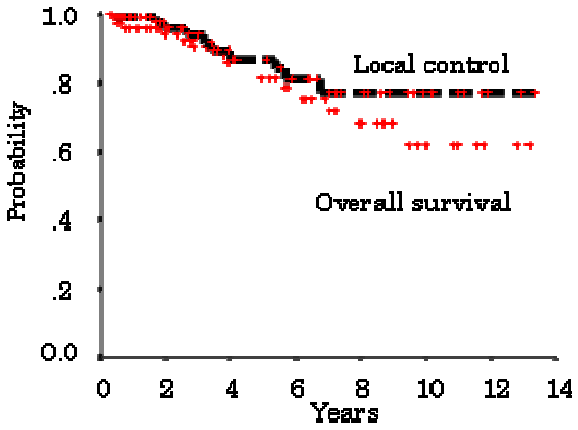

Fig. 1. The local control and overall survival of skull and paracervical cancer patients treated with carbon ion radiotherapy (n=76).

3. Chordomas

Of the 76 patients, 44 patients (58 %) had chordomas. The 5-year local control and overall survival rates of these patients were 88% and 87%, respectively. Of the 44 patients, 6 patients developed in-field recurrence. The local recurrence (in-field) patterns for chordomas were analyzed (Table 1). All of the recurrent sites were located on the edge of the tumors. There were no patients with in-field recurrence from the center of the tumor. Of the 6 who developed in-field recurrence, 4 of the sites were very close to an organ at risk, such as the brain stem or spinal cord.

Table 1. Local recurrence patterns of chordomas

	Age	Gender	Tumor location	Dose (GyE)	Recurrent site
1	47	F	P	48.0	Marginal (spinal cord)
2	64	F	P	57.6	Marginal (pharynx)
3	63	M	P	60.8	Marginal (pharynx)
4	67	F	P	60.8	Marginal (spinal cord)
5	47	F	S	52.8	Marginal (brain stem)
6	30	M	S	60.8	Marginal (brain stem)

* P: paracervical, S: skull base

Discussion

A carbon ion dose of 60.8GyE shows excellent local control. Additionally, we did not observe any severe toxicity to critical organs, such as the brain stem, spinal cord or optic nerves at any of the doses used. Beginning in April 2004, a phase II trial using carbon ion radiotherapy was initiated under the Highly Advanced Medical Technology scheme with an irradiation schedule of 60.8 GyE in 16 fractions over 4 weeks.

High LET charged particles such as carbon ions have excellent dose localizing properties, and this can cause severe damage to the tumor while minimizing the effect on normal tissues. When the tumor was located close to critical organs, delineation of the clinical target volume was done in an effort to prevent damage to these organs. In particular, when both optic nerves were involved in the high dose area, treatments were planned to spare the contralateral optic nerve and chiasm based on our previous dose criteria [1]. For tumors close to the brain stem or spinal cord, we recommended surgical resection to create a space between the tumor and these organs before carbon ion radiotherapy was administered. This allowed for better prevention of severe toxicity to the brain stem and spinal cord, and may have improved the local control rate, because most local recurrences arise from the marginal site adjacent to the critical organs. Tumors such as chordomas can only be judged on the results of the long-term prognosis. Consequently, it will take more time to reach a definitive conclusion about the efficacy of the carbon ion radiotherapy in our series of patients. However, it is already clear that, compared with photon or other charged particle radiotherapy, carbon ion radiotherapy will provide higher local control rates with lower toxicity to the surrounding normal tissues (Table 2) [2-14].

Table 2. The clinical characteristics of the reported cases of skull base chordoma

			Median	Median f/u	Local control rate (%)		
	Authors	N	dose	(y)	3-y	5-y	10-y
Photon	Catton et al . [4]	24	50	5.2		23	15
	Romero et al. [5]	18	50	3.1		17	
	Forsyth et al. [6]	39	50	8.3		39	31
	Magrini et al. [7]	12	58	6		25	25
Proton (+/- photon)	Munzenrider et al. (MGH) [8]	169	66-83	3.4		73	54
	Noel et al (CPO) [9]	100	67	2.6	86 (2y)	54 (4y)	
	Igaki et al. (Tsukuba) [10]	13	72	5.8	67	46	
	Ares et al. (PSI) [11]	42	73.5	3.2 (mean)		81	
Helium	Castro et al. (LB) [12]	53	65	4.3		63	
Carbon	Shults-Ertner et al. (GSI) [13]	96	60	2.6 (mean)	81	70	
	NIRS [14]	39	60.8	4.7		82	82

Conclusions

In this phase I/II clinical study for skull base and paracervical tumors, a dose escalation study was performed up to the fourth-stage dose level. Finally, a dose fractionation regimen of 60.8GyE in 16 fractions over 4 weeks was recommended. Our data from a phase I/II study have demonstrated that a carbon ion dose 60.8GyE was effective and safe for the treatment of skull base and paracervical tumors.

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Carbon Ion Radiotherapy in a Hypofraction Regimen for Stage I Non-Small Cell Lung Cancer

Naoyoshi Yamamoto, Masayuki Baba, Mio Nakajima, Kyosan Yoshikawa, Naruhiro Matsufuji, Shinichi Minohara, Hiroshi Tsuji, Tadashi Kamada, and Hirohiko Tsujii

Hospital, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
e-mail address: nao_y@nirs.go.jp

Abstract

From 1994 to 1999, we conducted a phase I/II clinical trial for patients with stage I non-small cell lung cancer (NSCLC) by using carbon ion beams alone, demonstrating optimal doses of 90.0GyE in 18 fractions over 6 weeks (Protocol #9303) and 72.0GyE in 9 fractions over 3 weeks (Protocol #9701), which achieved a more than 95% local control rate with minimal pulmonary damage. In the present study, the total dose was fixed at 72.0GyE in 9 fractions over 3 weeks (Protocol #9802), and at 52.8GyE for stage IA and 60.0GyE for stage 1B in 4 fractions in 1 week (Protocol #0001). Following this schedule, we conducted a phase II clinical trial for stage I NSCLC from 1999 to 2003. We also conducted a phase I/II single fractionation clinical trial (Protocol #0201) as a dose escalation study. The total dose was initially 28.0GyE in 2003, and it was increased to 50.0GyE in 2011. This article describes the intermediate steps. Most targets were irradiated from four oblique directions. A respiratory-gated irradiation system was used for all sessions. Local control and survival were assessed by the Kaplan-Meier method. For statistical testing, the Log-rank test was used.

The local control rate for all patients (#9802 and #0001) was 91.5%, and those for T1 and T2 tumors were 96.3% and 84.7%, respectively. While there was a significant difference (p=0.0156) in the tumor control rates between T1 and T2 tumors, there was no significant difference (P=0.1516) between squamous cell carcinomas and non-squamous cell carcinomas. The 5-year cause-specific survival rate was 67.0% (IA: 84.4, IB: 43.7), and the overall survival was 45.3% (IA: 53.9, 1B: 34.2). No adverse effects greater than grade 2 occurred in the lungs.

In a single fractionation trial, the 5-year local control rate for 131 patients was 80.5%, and the control rates for T1 and T2 tumors were 82.8% and 78.4%, respectively. No adverse effects greater than grade 2 occurred in the lungs.

Carbon beam radiotherapy, an excellent new modality in terms of high QOL and ADL, was proven to be a valid alternative to surgery for stage I NSCLC, especially for elderly and inoperable patients.

Introduction

In 1998, lung cancer became the leading cause of cancer-related death in Japan, as it had been in Western countries. Surgery plays a pivotal role in the curative treatment for non-small cell lung cancer (NSCLC), but it is not necessarily the best treatment for elderly persons and/or patients with cardiovascular and pulmonary complications. Conventional radiotherapy as an alternative, however, leads to a five-year survival rate in merely 10-30% of the patients due to poor control of the primary tumor. Dose escalation is essential to improve the efficacy of radiotherapy, but this involves an increasing risk of pulmonary toxicity. Carbon ion radiotherapy (CIRT) is a promising modality because of its excellent dose localization and high biological effect on the tumor. Our clinical trials led us to conclude that irradiation with heavy particle beams, notably carbon ion beams, offers

a significant potential for improving tumor control without increasing the risk of toxicity.

Between 1994 and 1999, a phase I/II study of the treatment of stage I NSCLC by CIRT was first conducted using a dose escalation method to determine the optimal dose. An additional purpose was to develop correct, reliable and safe irradiation techniques for CIRT for the treatment of NSCLC. As reported in our phase I/II study [1], the following results (Table 1) were obtained: 1) The local control rate was dose-dependent, reaching more than 90% at 90.0GyE with a regimen of 18 fractions over 6 weeks, and at 72.0GyE given in 9 fractions over 3 weeks. Both doses were determined to be optimal. It was found that setting the provisional target by allowing for the differences in the CT values can prevent marginal recurrence [2]. 2) Damage to the lungs in this study was minimal, with grade 3 radiation pneumonitis occurring in 2.7% of the cases. Respiratory-gated and 4-portal oblique irradiation directions, excluding opposed ports, proved successful for reducing the incidence of radiation pneumonitis. 3) The patient survival was strongly influenced by the local control and tumor size of the primary lesion. The early detection of nodal and intralobar metastasis, followed by irradiation with carbon beams, can help ensure a better survival rate. Local failure, distant metastasis and malignant pleurisy were responsible for decreases in survival.

Adverse reactions in the lungs
1) minimum damage to lungs (grade 3 radiation pneumonitis in 2.7% of patients)
2) influenced by dose, respiratory movement, and port direction and number
Local control
1) dose-dependent, but less dependent on tumor size and histological type
2) more than 90% by the optimal dose, and demonstrated by the pathological CR
Survival
1) influenced by the local control status and tumor size
2) less decreased by nodal and intralobar metastasis, but more by local failure, malignant pleurisy and distant metastasis

Table1. The results of the phase I/II study of carbon beam radiotherapy for stage I non-small cell lung cancer

In the present study, a phase II clinical trial and a phase I/II dose escalation clinical trial were performed. In the phase II clinical trial, the total dose was fixed at 72.0GyE in 9 fractions over 3 weeks [3], and at 52.8GyE for stage IA NSCLC and 60.0GyE for stage IB NSCLC in 4 fractions administered during one week [4]. Using this optimal schedule, the phase II clinical trial was initiated in April in 1999 and closed in December in 2003, after accruing a total of 127 patients.

The phase I/II dose escalation clinical trial was initiated in April 2003. The initial total dose was 28.0GyE administered in a single fraction using respiratory-gated and 4-portal oblique irradiation directions, with the total irradiation dose being escalated in increments of 2.0GyE each, up to 50.0GyE. This clinical trial is still in progress. This article describes the intermediate steps of the phase I/II clinical trial and the preliminary results of the phase II clinical trial in terms of the local control and survival after CIRT.

Materials and Methods

[The phase II clinical trial]

One hundred and twenty-nine patients with 131 primary lesions were treated with CIRT. Fifty-one primary tumors of 50 patients were treated by carbon ion beam irradiation alone using a fixed total dose of 72GyE in 9

fractions over 3 weeks (#9802 protocol [3]). The remaining 79 patients had 80 stage I tumors (#0001 protocol [4]). For the analysis of survival, 127 patients were evaluated, as 2 patients had been treated twice, one in the first protocol #9802, and one in the second protocol #0001. The patients with IA and IB stage tumors were treated with fixed doses of 52.8GyE and 60.0GyE in 4 fractions in one week, respectively. Their mean age was 74.5 years, and the gender breakdown was 92 males and 37 females. The tumors included 72 T1 and 59 T2 tumors, with a mean tumor diameter of 31.5 mm, By type (determined by biopsy), there were 85 adenocarcinomas, 43 squamous cell carcinomas, 2 large cell carcinomas and 1 adenosquamous cell carcinoma. Medical inoperability was diagnosed for 76% of the lesions.

[The phase I/II clinical trial (single fractionation)]

One hundred and thirty-one patients were treated in this clinical trial between April 2003 and August 2010. As mentioned above, the intermediate steps of this still ongoing phase I/II clinical trial included a total dose of 36.0GyE or more, and the follow-up time was 6 months or more after CIRT. The local control rate was as high as 80%. The 131 primary tumors of the 131 patients were treated by carbon ion beam irradiation alone using a total dose of 36.0GyE (n=18), 38.0GyE (n=14), 40.0GyE (n=20), 42.0GyE (n=15), 44.0GyE (n=44) or 46.0GyE (n=20) per single fractionation. The mean patient age was 73.6 years, and the gender breakdown was 43 females and 88 males. The tumors were 78 T1 and 53 T2 tumors with a mean diameter of 29.0 mm . By type (cancer type was determined by biopsy), there were 90 adenocarcinomas, 40 squamous cell carcinomas, and one large cell carcinoma. Medical inoperability diagnosed in 57.3% of cases (Table 2).

Age (mean)		46-87 (73.6)
Gender	Female	43
	Male	88
PS	0	99
	1	31
	2	1
Tumor size (mean)		10-62 (29.0)*
Stage	IA	78
	IB	53
Histology	Adenoca.	90
	Sq cell ca.	40
	Large cell ca.	1
Reason for inoperability		
	Refusal	56 (42.7)**
	Medically inoperable	75 (57.3)**
Total dose (GyE)		
	36.0	18
	38.0	14
	40.0	20
	42.0	15
	44.0	44
	46.0	20

*mm, **percent Aug. 31, 2010

Table2. The treatments and characteristics of the 131 patients with stage I NSCLC

[Carbon ion beam irradiation]

The same system for carbon ion beam irradiation was used in both the phase II and phase I/II clinical trials. The targets were usually irradiated from four oblique directions without prophylactic elective nodal irradiation

(ENI). A greater than 10-mm margin was set outside the gross target volume (GTV) to determine the clinical target volume (CTV). The planning target volume (PTV) was established by adding an internal margin (IM) to the CTV. The IM was determined by extending the target margin in the head and tail direction by a width of 5 mm,
leading to a successful prevention of marginal recurrence possibly resulting from respiratory movement [2]. Fig. 1 shows the dose distribution maps for a representative case. A respiratory-gated irradiation system was used in all irradiation sessions. Fig. 2 shows the CIRT room. We used vertical or horizontal beams in 2 oblique positions, including a total of 4 irradiation directions.

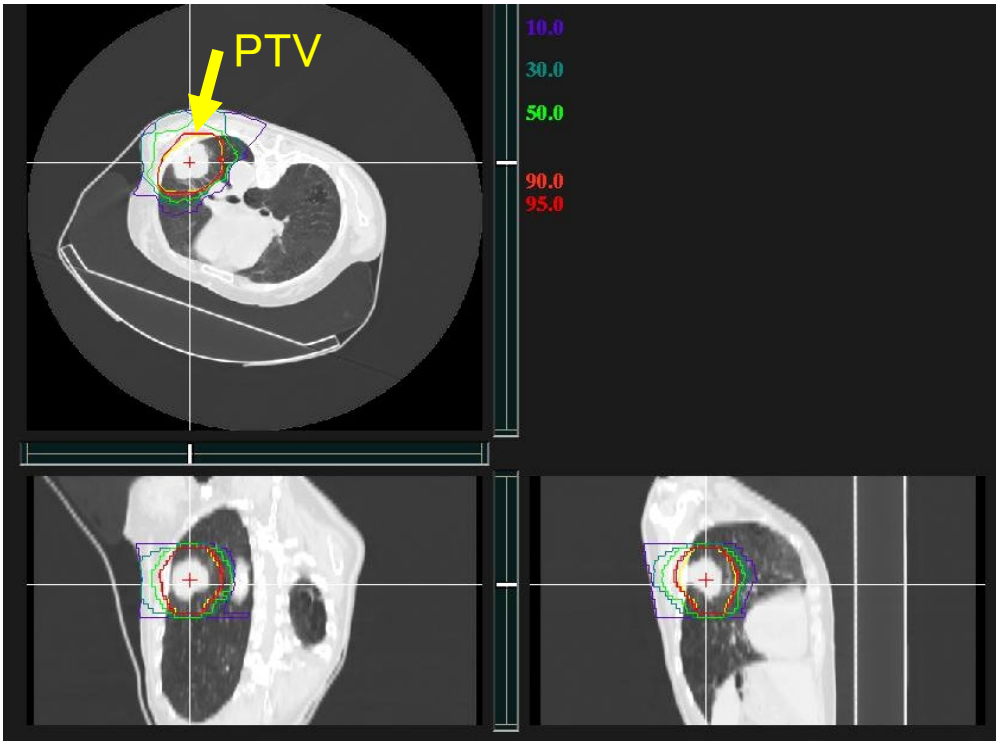

Fig. 1. Dose distribution maps for a 71-year-old female

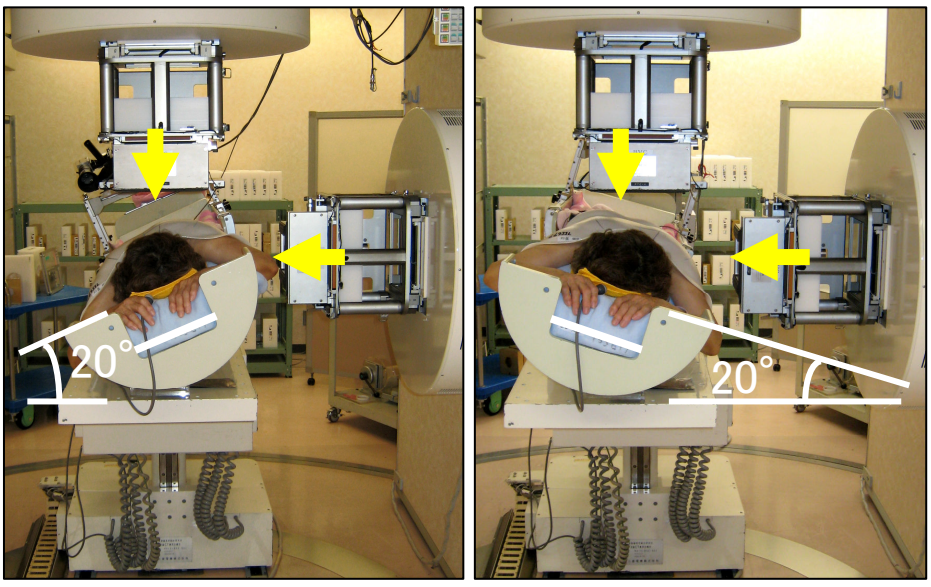

Fig.2. The CIRT treatment room

[Statistical analysis]

The local control and survival rates were assessed by the Kaplan-Meier method. For statistical analyses, the Log-rank test was used.

Results

[The phase II clinical trial (#9802, #0001)]

All patients were followed up until death, with a median follow-up time of 50.8 months, ranging from 2.5 months to 70.0 months. The local control rate for all 131 primary lesions was 91.5% (Fig. 3), while those for T1 (n=72) and T2 (n=59) tumors were 96.3% and 84.7%, and for the squamous cell type (Sq) (n=43) and non-squamous cell type (Non-Sq) (n=88) were 87.1% and 93.8%, respectively. While there was a significant difference (p=0.0156) in the tumor control rate between T1 and T2 tumors, there was no significant difference (P=0.1516) between the results for squamous and non-squamous cancers within the T1 group, nor between theT1 and T2 groups. However, with respect to squamous cell cancer, the local control was 100% for T1 (n=17) and 78.0% for T2 (n=26) tumors, which was nearly significant (p=0.0518). The local control rate for non-squamous tumors was 95.3% for T1 (n=55) and 91.0% for T2 tumors (n=33), which was not significantly different (p=0.3364).

The 5-year cause-specific survival rate of the 127 patients was 67% (Fig. 3), breaking down into 84.8% for stage IA and 43.7% for stage IB tumors (Fig. 4A). The 5-year overall survival rate was 45.3% (Fig. 3), breaking down into 53.9% for stage IA and 34.2% for stage IB tumors (Fig. 4B).

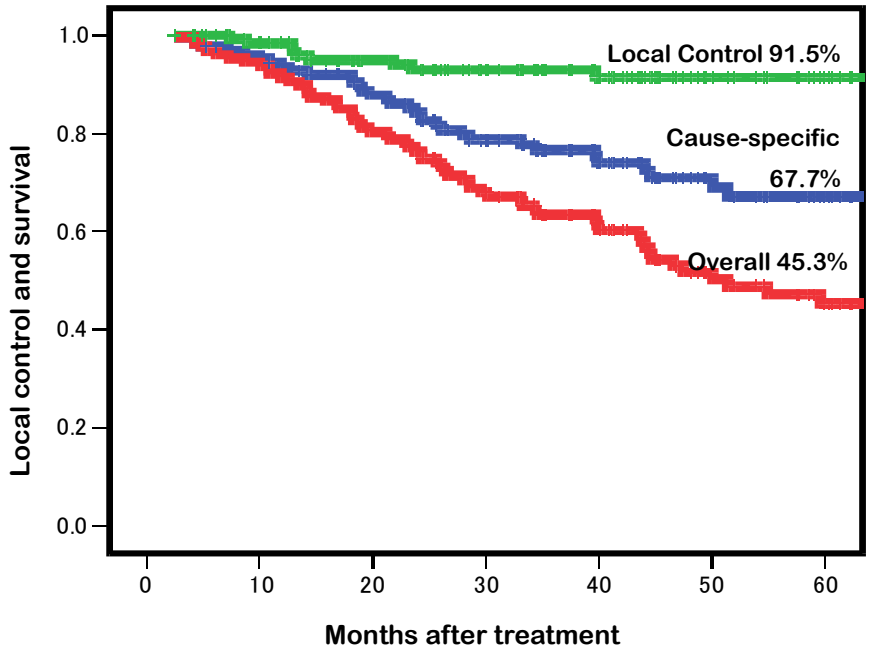

Fig. 3. The local control (n=131) and survival (n=127) rates after CIRT

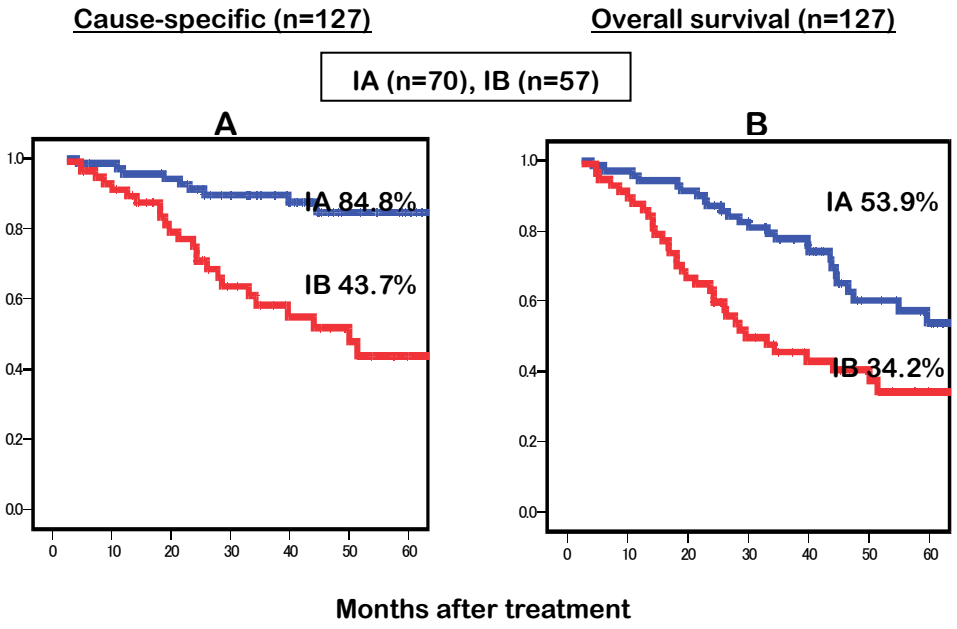

Fig. 4. The survival rates of patients by stage (IA vs IB)

The toxicities to the skin and lungs caused by CIRT were assessed according to the RTOG (early) and RTOG/EOTRC (late) as shown in Tables 3 and 4. Early skin reactions were assessed for 131 lesions and late skin reactions for 128 lesions. Of the early reaction lesions, 125 were grade 1 and 6 were grade 2. Among the late reaction , 126 were grade 1, 1 was grade 2, and 1 was grade 3. Lung reactions were clinically assessed in 129 patients. One hundred twenty-seven had grade 0 and 2 had grade 2 early reactions. Late effects were followed up in 126 patients: 7 patients had grade 0, 116 patients had grade 1, and 3 patients had grade 2 reactions. No adverse events higher than a single grade 2 reaction were observed.

Table 3. Adverse skin reactions following CIRT

Skin		Early reaction (RTOG)						Late reaction (RTOG)					
		Lesion	Grade					Lesion	Grade				
		No.	0	1	2	3	≧4	No.	0	1	2	3	≧4
	#9802	51	0	50	1	0	0	51	0	49	1	1	0
	#0001	80	0	75	5	0	0	77*	0	77	0	0	0
	Total	131	0	125	6	0	0	128	0	126	1	1	0

* 3 cases were not observed due to early death

Fifty-three of the 127 patients (41.7%) developed a recurrence, all occurring between 1 and 54 months (median, 10.5 months) after the commencement of therapy. No occurrence was observed in the other 74 patients (58.3%). The 9 primary recurrences (7.1%) and 11 regional metastases (8.7%) consisting of 7 regional nodes (5.5%), one intrabronchial (0.8%), and 3 intralobar metastases (PM1) (2.4%) occurred in the loco-regional site. In one patient, the primary recurrence was seen at the margin, while in another it occurred in-field.

Table4 . Adverse lungs reactions following CIRT

Skin		Early reaction (RTOG)						Late reaction (RTOG)					
		Lesion	Grade					Lesion	Grade				
		No.	0	1	2	3	≧4	No.	0	1	2	3	≧4
	#9802	50	49	0	1	0	0	50	0	48	2	0	0
	#0001	79	78	0	1	0	0	76*	7	68	1	0	0
	Total	129	127	0	2	0	0	126	0	116	3	0	0

* 3 cases were not observed due to early death

Based on the sub-stage classification, the incidence of loco-regional recurrence, pleural dissemination, and distant metastasis for stage IB (63%) was much higher than that for IA (24%). The total incidence of first recurrence for stage IB (63%) also tended to be higher than that for stage IA (24%). Verification by the $\chi 2$ test showed no significant difference ($\chi 2=1.63$).

The causes of death in the patients were as follows: 62 out of the 127 patients (48.8%) died, half of disease progression. Among the patients with recurrence, 5 of the 9 with primary recurrence (55%) died from disease progression. Ten of the 11 patients with regional metastases were re-treated, 9 with CIRT and 1 with photons. Seven of these patients, although they had no further recurrence, died due to intercurrent disease, and 1 with node metastasis but no re-treatment died of disease progression. Eight of the 11 patients with regional metastases (72%) died, and 9 of the 10 patients (90%) with malignant pleurisy and 17 of the 23 patients (74%) with distant metastases died of disease progression. Five of them died due to primary recurrence, and 26 due to metastasis and dissemination. For the remaining 31 patients, intercurrent diseases were the cause of death [3, 4].

[The phase I/II clinical trial (single fractionation)]

All patients were followed up until death, with a median follow-up time of 35.2 months, ranging from 1.6 months to 68.4 months. The 5-year overall local control rate for the 131 primary lesions was 80.5%, and those for the T1 (n=78) and T2 (n=53) tumors were 82.8% and 78.4%, respectively (Fig. 5). The overall survival rate was 52.6% and the cause-specific survival rate was 71.5%.

The toxicities of CIRT to the skin and lungs were assessed according to NCI-CTC (early) and RTOG/EOTRC (late) as shown in Tables 5 and 6. Early skin reactions were assessed for 131 lesions and late skin reactions for 128 lesions. Of the early reaction lesions, 126 were grade 1 and 3 were grade 2. Among the late reaction lesions, 123 were grade 1 and one was grade 2. Lung reactions were clinically assessed in the 131 patients. Forty-seven had grade 0, 83 had grade 1 and one had grade 2 among early reactions. Late reactions were followed up in 126 patients, with 114 showing grade 1 and one showing a grade 2 reaction.

The clinical course of a representative 71-year-old female is shown in Figs. 6 and 7. Tumor shrinkage and slight lung fibrosis were apparent, and a grade 1 skin reaction was observed.

Discussion

In the present study, the local control, cause-specific, and overall survival rates for the 127 patients in the phase II clinical trial were 91.5%, 67.0%, and 45.3%, respectively. Also, the overall local control, local control in T1 tumors, and local control in T2 tumors were 80.5%, 82.8%, and 78.4%, respectively, by single fractionation. The toxicities to the skin, lungs and bone were minimal.

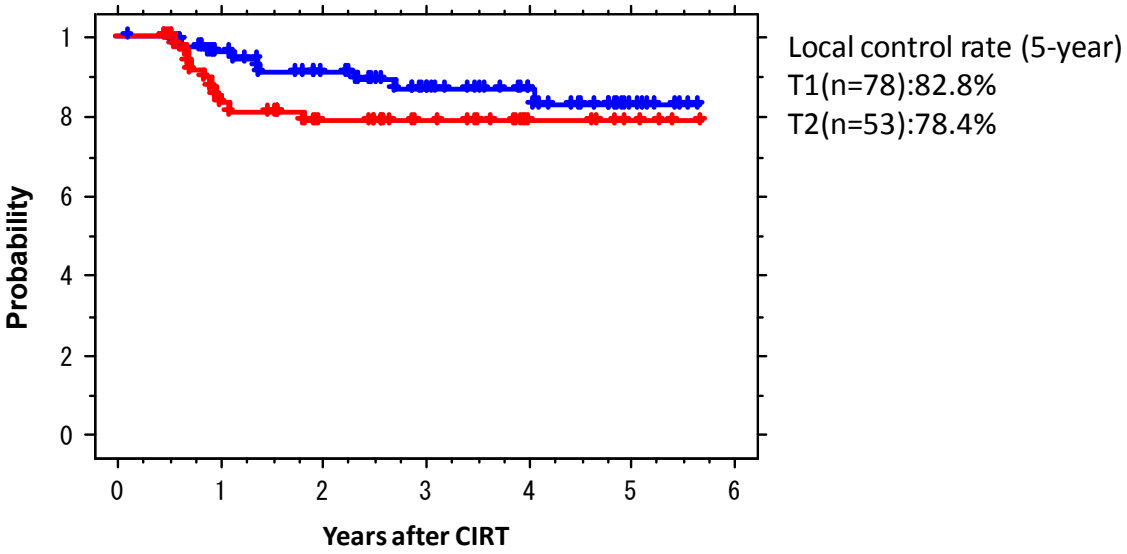

Fig.5. The tumor control rates after CIRT using single fractionation

Table5. The incidence of adverse skin reaction after CIRT using single fractionation

Skin	Total dose (GyE)	Early reaction (NCI-CTC)						Late reaction (RTOG/EORTC)					
		No. of Case	Grade					No. of Case	Grade				
			0	1	2	3	≧4		0	1	2	3	≧4
	36.0	18	0	18	0	0	0	17*	0	17	0	0	0
	38.0	14	0	14	0	0	0	13*	0	13	0	0	0
	40.0	20	1	18	1	0	0	20	2	17	1	0	0
	42.0	15	0	15	0	0	0	14	1	14	0	0	0
	44.0	44	1	41	2	0	0	43*	1	42	0	0	0
	46.0	20	0	20	0	0	0	20	0	20	0	0	0
	Total	131	2	126	3	0	0	128	4	123	1	0	0

*One case was not observed in each group

Table 6. Adverse lung reactions after CIRT using single fractionation

Lung	Total dose (GyE)	Early reaction (NCI-CTC)						Late reaction (RTOG/EORTC)					
		No. of Case	Grade					No. of Case	Grade				
			0	1	2	3	4=<		0	1	2	3	4=<
	36.0	18	12	6	0	0	0	17*	2	15	0	0	0
	38.0	14	9	5	0	0	0	13*	2	11	0	0	0
	40.0	20	10	10	0	0	0	19*	4	15	0	0	0
	42.0	15	10	5	0	0	0	14*	1	14	0	0	0
	44.0	44	6	37	1	0	0	44	2	40	1	0	0
	46.0	20	0	20	0	0	0	19*	0	19	0	0	0
	Total	131	47	83	1	0	0	126	11	114	1	0	0

*One case was not observed in each group

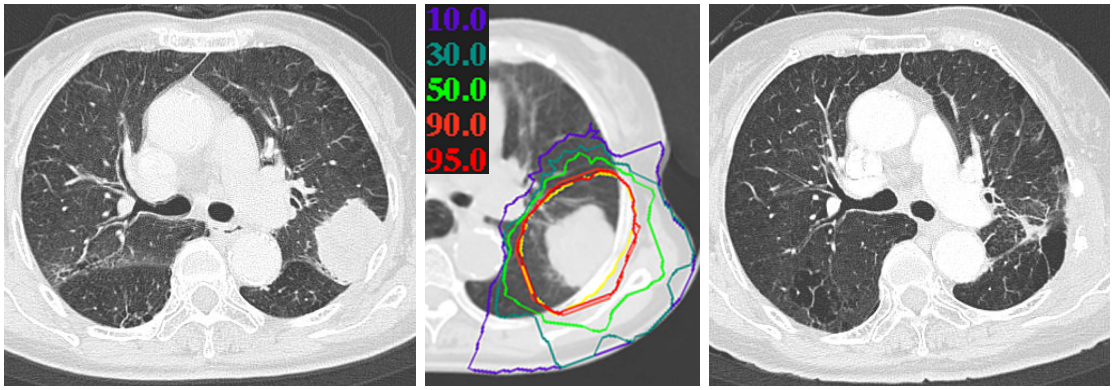

Fig. 6. The clinical course of 71-year-old female (T2N0M0 squamous cell carcinoma) after CIRT (40GyE/ single fractionation). An initial CT scan (A), dose distribution map (B), and a CT scan (C) taken 18 months after CIRT are shown. Apparent tumor shrinkage was observed

Out of the 131 primary cancers in 127 patients, local recurrence developed in 9 patients (6.8%). The average time of recurrence was 17.2 months, ranging from 7 to 39 months. According to our previous study, the observation period required to determine local control of the irradiated lesions was at least 3 years post- therapy [1]. However, the present study suggested the need for a longer observation period. It is evident that prolonged survival guarantees a more reliable observation of the local control results.

To correctly assess the local control rate of patients who could not be observed for such a long duration because of death resulting from metastasis/dissemination or intercurrent disease, a histological approach based on repeated bronchoscopy was used, providing evidence of the absence of viable tumor cells in the collected specimens [3]. Furthermore, definite tumor control was also confirmed by the autopsies of CIRT-treated patients and in cases treated by surgery [5]. Such high and definite tumor control appears to be an outstanding feature of CIRT. Presumably, this is primarily due to the radiobiological nature of the high LET beams, which may account for the higher survival rate of stage I NSCLC patients. On the other hand, the failure of local control for primary tumors directly affected the poor survival of stage I NSCLC patients [1, 3]. Among our cases, 5 of the 9 patients with primary recurrence (55%) died due to disease progression.

Eleven regional recurrences were detected. This incidence was close to that of surgery (7.5% [6], 11% [7]). Eight of the patients (72%) died. Only one patient, who did not undergo retreatment, died due to disease progression. The other 7 retreated patients died due to intercurrent discase. Martini et al. [7] reported that any resection less than lobectomy and no lymph node dissection had adverse effects on recurrence and survival. In contrast, our treatment strategy for regional recurrence is thought to have gained validity compared to the standard surgical procedure for stage I NSCLC.

Nine of the 10 patients (90%) with malignant pleurisy and 17 of the 23 patients (74%) with distant metastasis died of disease progression. The poor prognosis of stage IB cases was the result of the high incidence of pleural and distant metastasis.

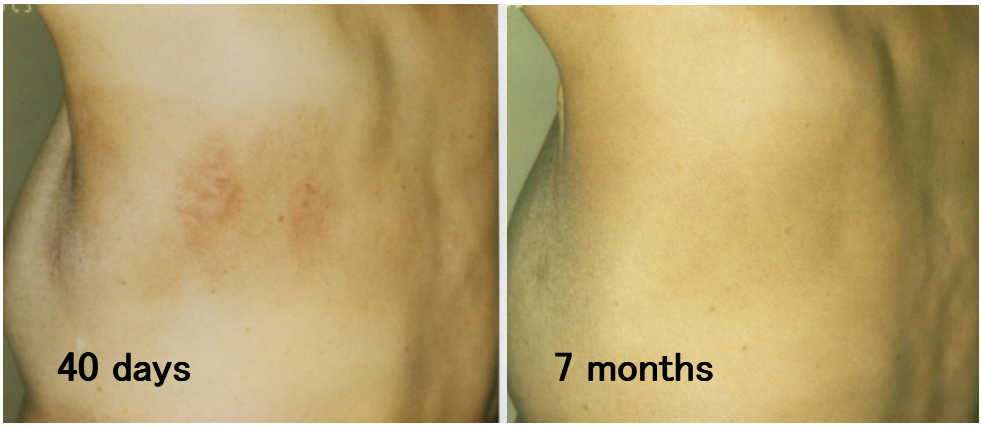

Fig. 7. A skin reaction after CIRT (40.0GyE/1fr) in the 71-year-old female.
A grade 1 reaction was observed.

For the patients with clinical stage I NSCLC, our 5-year overall survival results were somewhat inferior to those of surgery [3, 5]. This difference may be due to the significant age gap between the two groups. The incidence of death due to recurrence in the surgical groups in previous studies was 29% or 36%, whereas that due to intercurrent diseases was 19% or only a few percent [6, 7]. In contrast, our patients showed a higher incidence of death due to intercurrent diseases (60%) than death due to recurrence (40%). A comparison of stage IA with stage IB patients revealed that while there was a large difference between the overall (53.9%) and cause-specific (84.8%) survival in stage IA patients, there was a smaller difference in stage IB between the overall (34.2%) and cause-specific (43.7%) survival in stage IB patients. Such differences in the survival rates in the two stage I subgroups might be explained by the low incidence of recurrence-related death in stage IA patients(24%) and the relatively high incidence in stage IB patients (63%). The high frequency of intercurrrent death might be related to the advanced age of our patients, as they were on average 10 years older than the surgical patients [6, 7]. As we have reported previously, elderly patients 80 years and older can be treated safely by CIRT [8].

Compared with the pulmonary damage reported after stereotactic radiotherapy for stage I NSCLC [9-11], the incidence and severity of damage in our patients seemed to be remarkably low. These less severe and less common adverse effects on the lungs were likely achieved as a result of the small volume irradiated. This advantage results from the excellent dose distribution properties unique to carbon ion beams and the formation of a Bragg peak in contrast to the permeating beam associated with x-rays

Conclusions

One hundred twenty-seven stage I NSCLC patients with 131 primary tumors were treated with CIRT using a total dose of 72GyE in a regimen of 9 fractions over 3 weeks, and with 52.8GyE for stage IA and 60GyE for stage IB in 4 fractions over the course of one week. In addition, 131 stage I NSCLC patients with 131 primary tumors were treated with single-fraction CIRT using total doses ranging from 36.0GyE to 46.0GyE.

This study demonstrated seven major findings. First, the local control rate of the 131 primary lesions was 91.5%. There was a statistically siginificant difference between the local control rates for T1 and T2 tumors, and near significance between the rates for T2 squamous cell carcinoma versus T2 non-squamous cell carcinoma .

Second the 5-year overall and cause-specific survival rates of 127 patients were 45.3% and 67.0%, respectively. Third the 5-year overall survival rates of the patients with stage IA and stage IB disease were 53.9% and 34.2%, while the 5-year cause-specific survival rates of those with stage IA and stage IB were 84.8% and 43.7%,

respectively.

Fourth, there was high incidence of intercurrent death due to the advanced age and related complications in our patients. Fifth, the adverse effects on the skin and lungs were minimal, indicating the safety of the modality. Carbon beam radiotherapy, which is an excellent new modality in terms of a high QOL and ADL, is a valid alternative to surgery for stage I cancer, especially for elderly and inoperable patients. Sixth, in the trial of CIRT using single fractionation with a total dose range from 36.0GyE to 46.0GyE, the local control rate for the 131 primary lesions was 80.5%, and those for the T1 (n=78) and T2 (n=53) tumors were 82.8% and 78.4%, respectively. Finally, CIRT using single fractionation is effective, at least as viewed during an intermediate step, and is a safe treatment modality for stage I NSCLC patients.

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Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer

Shigeru Yamada, Makoto Shinoto, Satoshi Endo, Shigeo Yasuda, Hiroshi Imada, Tadashi Kamada and Hirohiko Tsujii

Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences

1. Characteristics of Locally Recurrent Rectal Cancer

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

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

Table 1. Resection and Survival Rates by Site of Recurrence

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

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

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

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

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

3. Study Treatment

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

4. Treatment Outcomes

(A) Normal-tissue Reactions

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

(B) Tumor response and Survival Rate

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

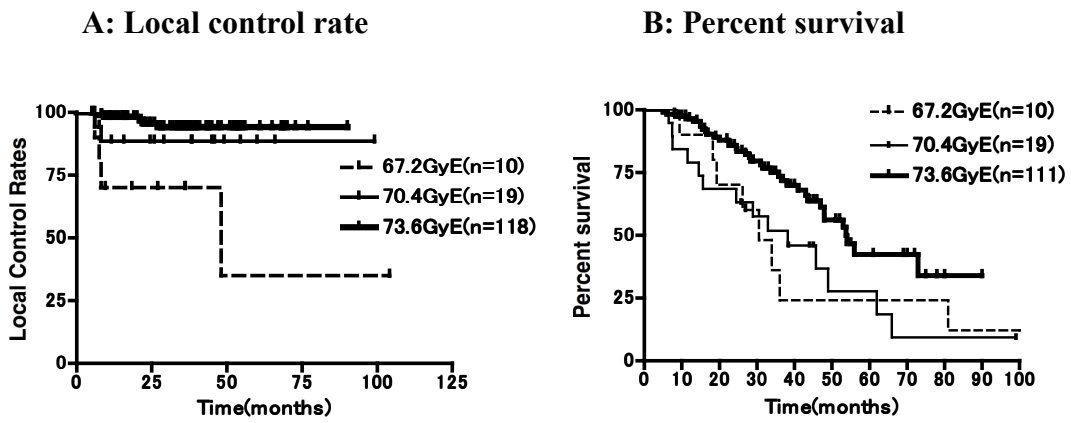

Figure 1. Results of Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer

(C) Comparison with Other Studies

The results of the patients treated with 73.6 GyE carbon ion radiotherapy were compared with those of other studies in which patients with locally recurrent rectal cancer were treated with other radiation therapies.[3-6] The results are summarized in Table 2.

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

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

Compared with the conventional radiation therapies yielding local control rates below 30% and 5-year survival rates below 10%, the carbon ion radiotherapy produced excellent results. Next, our results were compared with the surgical results reported from other institutions (Table 3).

Table 3. Results of Surgical Therapy for Patients with Locally Recurrent Rectal Cancer[7-9)]

Author (year)	No. of patients	1-Year survival	2-Year survival	5-Year survival
Kato 1994	32	93%	82%	46%
Garcia-Aguilar J1999	42	88%	62%	35%
Wanebo 1999	53	91%	62%	31%
Salo JC 1999	71	88%	75%	31%
Saito N 2003	43	91%	78%	39%
Moriya 2004	48	95%	76%	36%
NIRS 2010	**111**	**97%**	**86%**	**42%**

Our results were comparable to or higher than the published surgical results. In light of the fact that most of our cases involved unresectable tumors, our treatment yielded dramatically improved outcomes. In addition, the carbon ion radiotherapy provided a high quality of life for patients during and after treatment, because patients were spared from undergoing artificial sphincter insertion surgery, and were treated in the out-patient setting.

5. Carbon ion radiotherapy for locally recurrent rectal cancer in patients with prior pelvic irradiation

Among gastrointestinal malignancies, many studies have shown the safety and efficacy of pelvic reirradiation for rectal cancer [10-14]. Reirradiation to the pelvis could potentially play a role in palliation of symptoms or local control. Locally recurrences are located close to critical organs such as the small intestine, colon and bladder and in these patients reirradiation would be expected to be associated with a higher risk of acute and late toxicity at these organs than primary irradition.

The purpose of this study was to asses carbon ion radiation therapy performed as re-irradiation in patients with locally recurrent rectal cancer.

Twenty-three patients were treated with carbon ion RT as re-irradiation for locally recurrent rectal cancer. Nine relapses originated in the presacral region, 8 in the p for pelvic sidewalls and 6 in the perineal region. The total dose ranged of 70.4 gray equivalent (GyE) and was administered in 16 fixed fractions over 4 weeks (4.4 GyE/fraction).

All patients completed the scheduled treatment course. Grade 3 toxicities occurred in 6(26%) patients. The major late toxicities were peripheral neuropathy and infection.

No other severe acute reactions (grade $\geq$3) were observed at this study.

The one-year and three-year overall survival rates were 83% (95% CI, 68% to 98%) and 65% (95% CI, 43% to 87%), respectively. The one-year and three-year disease-free survival rates were 71% (95% CI, 51% to 91%) and 51% (95% CI, 27% to 75%), respectively.

Carbon ion radiotherapy as re-irradiation appears to be a safe and effective modality in the management of locally recurrent rectal cancer, providing good local control and offering a survival advantage without unacceptable morbidity.

6. Widening the Applicability of Carbon Ion Radiotherapy

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

7. Conclusion

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

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Carbon Ion Radiotherapy for Pancreatic Cancer

Makoto Shinoto, Shigeru Yamada, Shigeo Yasuda,Hiroshi Imada, Tadashi Kamada, Hirohiko Tsujii

Hospital of Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

e-mail address: shinoto@nirs.go.jp

<Background>

The number of deaths from pancreatic cancer in Japan exceeds 26,000 per year, and the number is increasing every year[1]. Pancreatic cancer is the fifth leading cause of cancer death and it is considered to be one of the most lethal cancers in Japan. Complete surgical resection is the only curative treatment. However, only a small percentage of patients (10-20%) are candidates for surgical resection because of local progression or metastatic spread at the time of diagnosis[2, 3]. Even if a curative resection is performed, the disease usually recurs and 5-year survival rates are less than 20% [4, 5].

Chemotherapy or chemoradiotherapy is selected as a standard treatment for unresectable pancreatic cancer. However, since pancreatic cancer is often resistant to chemotherapy or radiotherapy, the local control rate is very low. Recently, along with the development of new anticancer agents, the irradiation techniques have greatly progressed following the introduction of highly advanced radiotherapy. However, the outcome from therapy is still not satisfactory, with the median survival being approximately 10 months[6, 7]. We started phase I/II clinical trial for pre-operative carbon ion radiotherapy (CIRT) with 16 fractions in 4 weeks for resectable pancreatic cancer in 2000 (Figure 1).

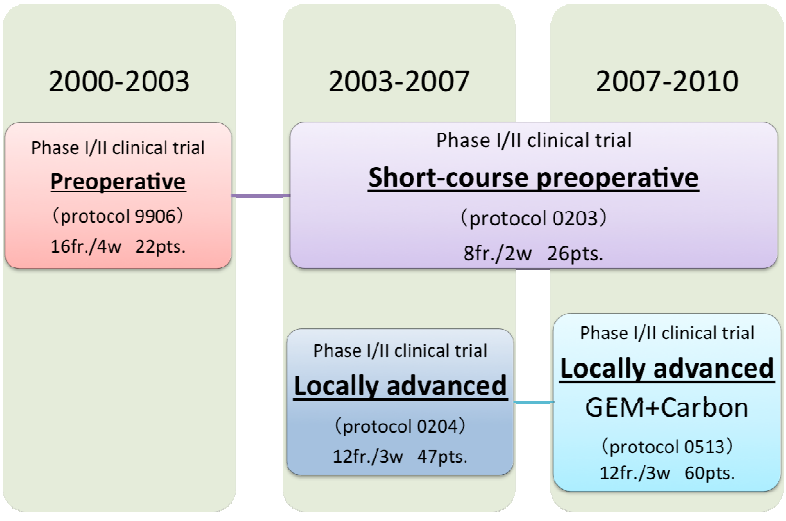

Figure 1. The clinical trial pathway of carbon ion radiotherapy against pancreatic cancer

The purpose of this treatment was to reduce the risk of postoperative local recurrence, which accounts for approximately 50% of total recurrences. We established the tolerance and effectiveness of preoperative CIRT and performed a clinical trial aimed at shortening the fraction size to 8 fractions in 2 weeks beginning in 2003 (Protocol 0203). In addition, we started phase I/II clinical trial for patients with locally advanced pancreatic cancer and showed that the treatment was safe and provided excellent local control rates. Accordingly, we are currently performing a clinical trial of using carbon ion radiotherapy combined with gemcitabine (Protocol 0513).

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

<Objective>

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

<Materials and methods>

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

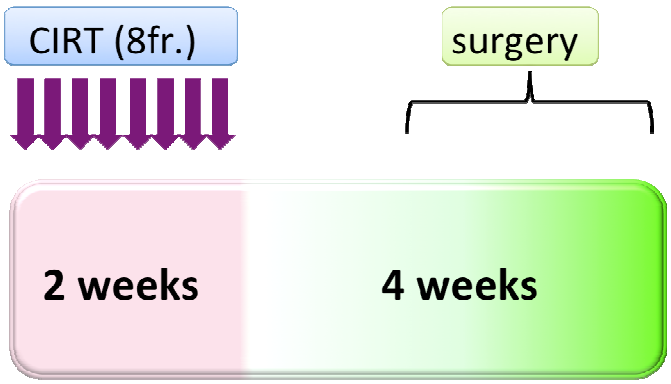

Figure 2. Schedule of preoperative CIRT and surgery (Protocol 0203)

<Results>

Twenty-six patients were registered from April 2003 through February 2010, and dose escalation was performed from 30GyE to 36.8yE (Table 1).

Table 1. Dose schedules of preoperative CIRT

CIRT (GyE)	No. of patients	No. of pts with resection
30.0	6	3
31.6	4	3
33.6	3	3
35.2	6	6
36.8	7	6

We have administered CIRT to all patients as scheduled. The clinical stage according to the UICC was stage IIA in 15 cases and stage IIB in 11 cases. Twenty-one out of 26 patients received curative resection (resection rate 81%), however, the remaining 5 patients did not undergo surgery due to liver metastases or refusal. Although grade 3/4 toxicities were noted in 2 patients (liver abscess-1, PV thrombus-1), both of them were unrelated directly to CIRT. No other serious adverse effects were observed. In the 21 surgical cases, the 5-year local control rates and overall survival rates were 100% and 53%, respectively.

＜Conclusion＞

Preoperative CIRT for patients with resectable pancreatic cancer appears to be acceptable toxicity. And preoperative CIRT reduces the risk of postoperative local recurrence and contributes to improvement of overall survival. This study did not reach the maximum tolerated dose but the dose at 36.8 GyE was estimated to be the recommended dose because of the sufficient local control rate.

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

<Objective>

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

<Materials and methods>

The eligibility criteria for this study were: locally advanced pancreatic cancer which involved the celiac trunk or superior mesenteric artery without distant metastasis. All patients had histologically- or cytologically-proven pancreatic adenocarcinoma or adenosquamous carcionoma. The radiation fractions were fixed at 12 fractions in 3 weeks, and the dose of gemcitabine and radiation were gradually increased. First, the dose was fixed at 43.2GyE/8 fractions and the gemcitabine dose was increased from 400, to 700 to 1000mg/m^2. Subsequently, the gemcitabine dose was fixed at 1000mg/m^2 and the radiation dose was increased by 5% increments (Figure 3). Gemcitabine was administered for 3 consecutive weeks, once a week (Figure 4). The irradiation field was set in the range that included the primary tumor, perineural lesions and prophylactic regional lymph node area.

CIRT*	GEM**
43.2GyE	400mg/m^2 ↓ 700mg/m^2 ↓ 1000mg/m^2
45.6GyE ↓ 48.0GyE ↓ 50.4GyE ↓ 52.8GyE	1000mg/m^2

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

Figure 3. The dose enhancement trial (Protocol 0513)

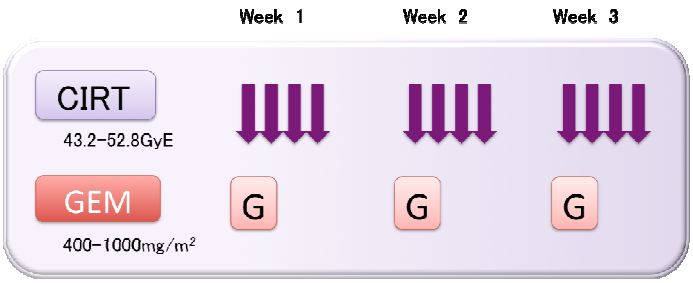

Figure 4. Treatment schedule (Protocol 0513)

<Result>

Sixty patients were registered from April 2007 through February 2011. The median age was 63 (range: 39-74) years. Performance status was 0 in 10 patients (17%), 1 in 48 (80%), and 2 in 2 (3%). The median serum CA19-9 level was 305.3 (range: 0.2-16830). Patients were treated with CIRT over five dose levels and concurrent weekly gemcitabine over three dose levels, an listed in Table 2.

Table 2. Dose schedule of CIRT with concurrent GEM

CIRT (GyE)	GEM (mg/m^2)	Number of patients
43.2	400	7
43.2	700	7
43.2	1000	12
45.6	1000	8
48.0	1000	8
50.4	1000	11
52.8	1000	11

Their clinical stage according to the UICC was stage III in 54 cases and stage IV in six cases. Dose limiting toxicity (DLT) developed as an early adverse event in three of 60 patients, which was a low incidence. One patients treated at the 50.4GyE dose level experienced grade 3 gastric ulcer 10 months after CIRT, but the patient recovered with conservative management. No other serious side effects were found. The combinations with full-dose gemcitabine (1000mg/m2) did not show any increased incidence of adverse effects with dose escalation. The two-year local control rate and two-year overall survival rate were 26% and 32% in all patients. The median survival time was 19.3 months. The Local control and overall survival by CIRT increased along with the dose escalation. In the high dose group, in which patients were irradiated with at least 45.6 GyE, the two-year local control rate and two-year overall survival rate were 47% and 66%.

<Conclusion>

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

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Carbon Ion Radiotherapy for Prostate Cancer

Hiroshi Tsuji, Nobutaka Mizoguchi, Shingo Toyama, Tadashi Kamada, Hirohiko Tsujii,
and the Working Group for Genitourinary Tumors

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
e-mail address:h_tsuji@nirs.go.jp

Abstract

Therapeutic outcome of hypofractionated conformal carbon ion radiotherapy towards localized prostate cancer was investigated. We analyzed the biochemical relapse-free rate of 1,084 cases which were observed for 6 months or more after carbon ion radiotherapy at the time of February 2011, also we analyzed survival rate, and the incidence of toxicity. 5-year biochemical relapse-free rate of whole cases was 90.6%. The Gleason score, PSA value and clinical stage were the significant prognostic factor of relapse-free rate. The difference of relapse-free rate by method of fractionation (20 fractions and 16 fractions) was not found. None but one out of 1,005 cases who were followed up at least 1 year developed grade 3 lower urological impairment, and incidences of grade 2 were 5.6% in lower urinary tract and 2.3% in the rectum, respectively. Furthermore, in the 16 fractions, the toxicity incidence was lower than 20 fractions. Accordingly, hypofractionation made it possible to reduce the toxicity incidence without reducing the relapse-free rate.

1.Introduction

As for the prostate cancer, recent irradiation therapy including brachytherapy, proton therapy and intensity modulated radiation therapy play active roles, and improving dose distribution and attendant dose escalation is showed to be connected to the outcome improvement. The National Institute of Radiological Sciences, Chiba, Japan (NIRS) has been challenging the prostate cancer treatment from June 1995 taking the advantage of the quality of carbon ion beam which has distinguished dose convergence and high anticancer efficacy. First, in order to establish an appropriate dose fractionation regimen for C-ion RT, two phase I/II clinical studies have been performed since 1994, using carbon ion beams generated by the Heavy Ion Medical Accelerator in Chiba (HIMAC). A phase II clinical study was then started in April 2000, using the established treatment method of hypofractionated C-ion RT with the recommended dose of 66.0GyE in 20 fractions over 5 weeks that had been proved effective in the phase I/II studies. The safety and efficacy of this treatment strategy of C-ion RT was further confirmed with this phase II study, and approval for its use as a highly advanced medical technology was obtained in November 2003. This article presents the methods and updated outcomes of this established C-ion RT, and also describes its future prospects at NIRS.

2. Materials and methods

We performed carbon ion radiotherapy against 1305 cases of prostate cancer from the start of clinical trial to February 2011. We treated 96 cases in the early dose escalation trials, 175 cases in the phase II clinical trial, thereafter 989 cases were treated in the approved highly advanced medical technology and 45 cases are in ongoing new clinical trial. The annual cases are gradually increasing, especially greatly increased in 2003 when we gained the approval of highly advanced medical technology and in 2007 when we shortened the therapy term from 20

times in 5 weeks to 16 times in 4 weeks (Figure 1).

The eligible patient had no metastases and pathological diagnosis was confirmed as prostate cancer case. As for the carbon ion radiotherapy, first we performed 20 fractions in 5 weeks and after establishing the appropriate dose of radiation and transferred to the highly advanced medical technology, we started 16 fractions in 4 weeks up to today. 562 out of 1305 cases are 20 fractions and 698 are 16 fractions. In a portion of cases, we started clinical trial of 12 fractions in 3 weeks, and have performed therapy for 45 cases.

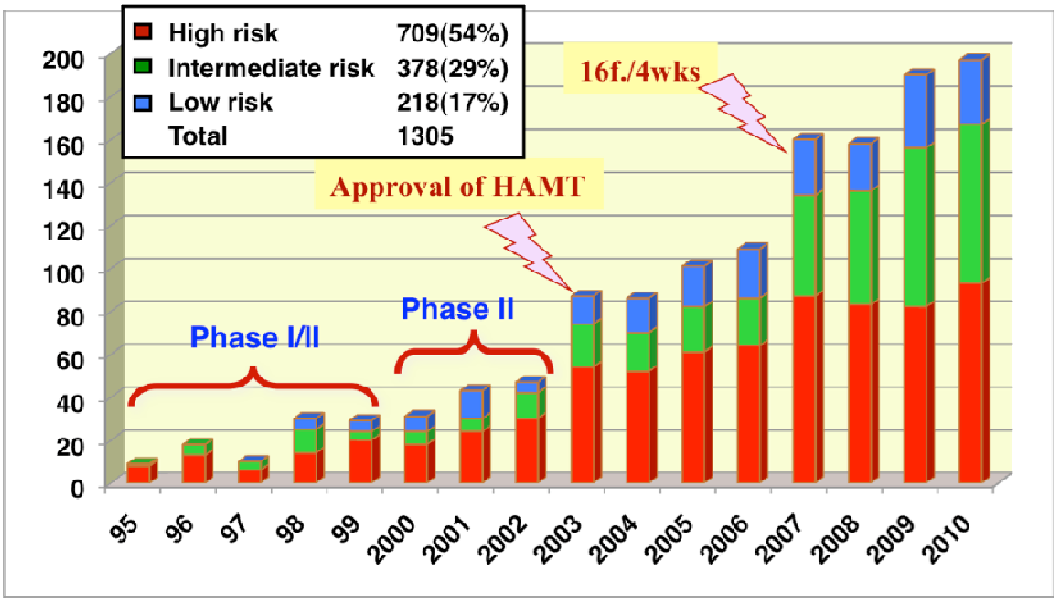

Figure 1. Transition by fiscal year of the number of prostate cancer carbon ion radiotherapy cases. (Risk group total)

In the current approach to therapy, the cases are classified into 3 groups (high risk, intermediate risk and low risk) according to the clinical stage, initial PSA value, and pathological Gleason score. For the high risk and intermediate risk groups, we combine long-term and short-term endocrine therapy, respectively (Figure 2). Among actual treated cases, high risk group account for more than a half of the whole cases (Figure 1).

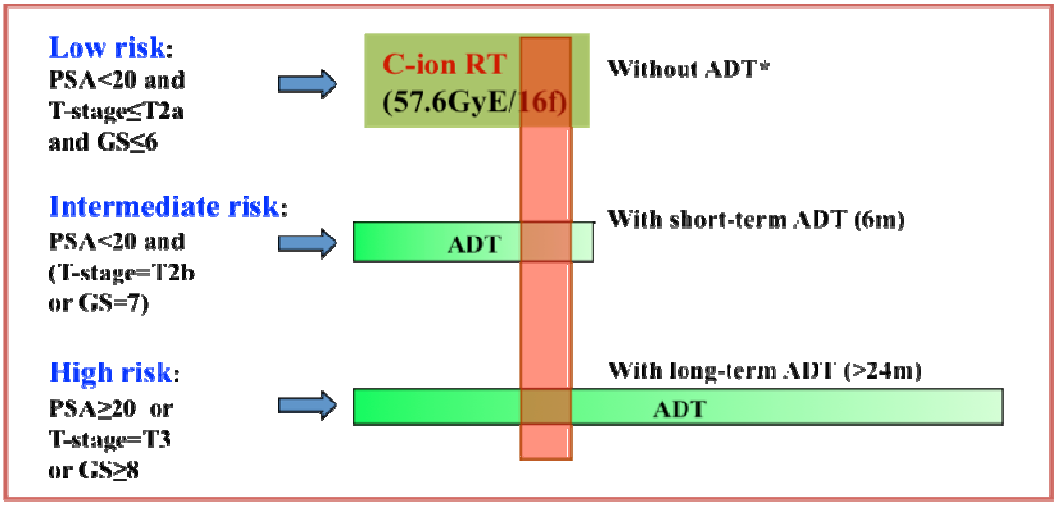

Figure 2. Current treatment strategy for prostate cancer at NIRS.
Patients were divided into three risk groups of high, intermediate, and low according to their T-stage, initial PSA, and Gleason score

For the treatment planning, a set of 2.5-mm-thick CT images was taken, with the patient placed in immobilization devices. Three-dimensional treatment planning was performed using HIPLAN software (National Institute of Radiological Sciences, Chiba, Japan). Clinical target volume (CTV) was defined as consisting of the prostate and the seminal vesicle (SV) demonstrated by CT images, irrespective of T-stage or other risk factors. MRI was also taken in all the patients and used as a reference for defining CTV. However, the whole SV should not always be included in the CTV, in the case of patients with a low risk. Thus, for example, the CTV of the patients staged as T1 or T2a did not cover the SV tips. Further, anterior and lateral safety margins of 10mm and a posterior margin of 5mm were added to the CTV to create the initial planning target volume (PTV-1). In order to reduce the dose to the anterior rectal wall, a rectum-sparing target volume (PTV-2) was used for the latter half of the C-ion RT, where the posterior margin was reduced to the anterior boundary of the rectum. Evaluation of the plan was routinely performed at the case conferences before the actual treatment, using the dose-volume histograms (DVH) for the CTV, PTV-1, PTV-2, and the rectum. Particularly, the DVH of the rectum was evaluated with comparing the reference DVH that was obtained from the analysis using actual DVH data of preceded dose-escalation studies. If the rectal DVH of the new patient was beyond the reference DVH at the high dose area, the treatment planning was revised. Fig. 3 shows the representative dose distribution.

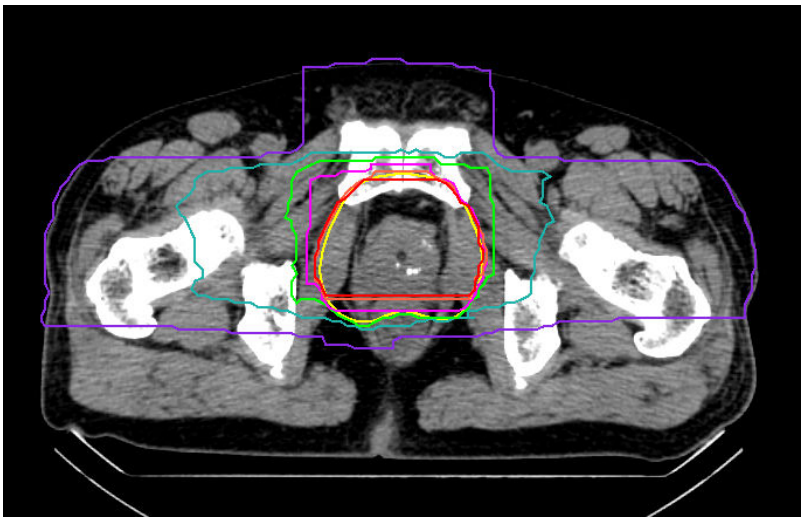

Figure 3. Representative dose distribution for prostate cancer at NIRS

The irradiated dose was fixed at 63.0GyE or 66.0GyE/20fractions as the recommended dose fractionation schedule established in the two previous phase I/II studies. In addition, more hypofractionated schedule of 57.6GyE/16fractionas was applied since September 2007. Furthermore, a new clinical trial of C-ion RT of 12 fractions over 3 weeks is also ongoing,. The analysis objects were treated by 20 fractions or 16 fractions after the phase II clinical trial and observed for 6 months and more.

3. Results

Of the 1305 patients treated until February 2011, 1084 patients who were treated in or after the phase II study were analyzed with regard to patient survival and biochemical relapse free rate judged according to the Phoernix criteria, PSA over nadir+2.0 = biochemical failure. Of those, 1005 cases who were observed 12 months or more were added up regarding an incidence of late radiation toxicity.

3-1） Toxicity

The result of comparison of late toxicity incidence on various radiotherapies and carbon ion radiotherapy is shown in Table 1, 2. Compared with other various radiotherapies, carbon ion radiotherapy exhibited lower rate toxicity incidence rate, especially, the significant low rate of rectal toxicity. As for the toxicity incidence rate of lower urinary tract system, the carbon ion radiotherapy of 63.0GyE/20 fractions, intensity modulated radiation therapy and proton were approximately the same, however, as for the 57.6GyE/16 fractions, lowering of the incidence rate was gained. As for the toxicity of the rectum, even in 63.0GyE it showed lower rate than X-ray or proton. 57.6GyE showed further lowering of the rate.

Table 1. Late gastrointestinal and genitourinary morbidity after C-ion RT in patients followed up more than 12 months

Dose GyE/f.	No.pts.	Rectum				Bladder/urethra			
		Grade0	G1	G2	G3	Grade0	G1	G2	G3
66.0/20250	195	47	8	0	101	115	34	0	
	(%)	(78.0)	(18.8)	(3.2)	(0)	(40.4)	(46.0)	(13.6)	(0)
63.0/20216	184	27	5	0	110	93	12	1	
	(%)	(85.2)	(12.5)	(2.3)	(0)	(50.9)	(43.1)	(5.6)	(0.5)
57.6/16539	505	31	3	0	305	224	10	0	
	(%)	(93.7)	(5.8)	(0.6)	(0)	(56.6)	(41.6)	(1.9)	(0)
Total	1005	884	105	16	0	516	432	56	1
	(%)	(88.0)	(10.4)	(1.6)	(0)	(51.3)	(43.0)	(5.6)	(0.1)

Table 2. Incidence of Late Radiation Toxicity in various radiotherapy for Prostate

Institutes	Radiotherapy	Dose(Gy/f)	No. of pts.	Morbidity ≥ G2	
				Rectum	GU
Christie H.[1)]	IMRT	60/20	60	9.5%	4.0%
Princess Margaret H.[2)]	IMRT	60/20	92	6.3%	10.0%
Cleveland CF.[3)]	IMRT	70/28	770	4.4%	5.2%
Stanford U.[4)]	SRT	36.25/5	41	15.0%	29.0%
RTOG9406[5)]	3DCRT	68.4-79.2/38-41	275	7-16%	18-29%
	3DCRT	78.0/39	118	25-26%	23-28%
Loma Linda U.[6)]	Proton	75.0/39	901	3.5%	5.4%
NIRS	Carbon	63.0/20	216	2.3%	6.1%
	Carbon	57.6/16	539	0.6%	1.9%

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

3-2）Relapse-free rate and survival rate

The Kaplan-Meier estimates of overall and biochemical relapse free (bNED) survivals for the 1084 patients at five years were 95.4% and 90.6%, respectively (Fig.4). By the date of analysis, 46 patients had died, 11 of metastasis from the prostate, and 35 of other malignancies or intercurrent diseases. So far, no patient belonging to the low-risk and intermediate-risk groups has died of prostate cancer.

A total of seven patients, three presenting with slowly elevated PSA and positive biopsies at 24 months, 38 months, and 48 months after C-ion RT, and four with apparent growth of tumor on the MRI images, were judged as having local recurrence. By the date of analysis, 72 patients met the Phoenix criteria of biochemical failure: more than 2.0 ng/ml rise of PSA from the nadir. Of these 72 patients, 31 patients were diagnosed as having metastasis, 7 were judged as having local recurrence, and the remaining 34 patients had no clinical evidence of recurrent lesions at the date of analysis.

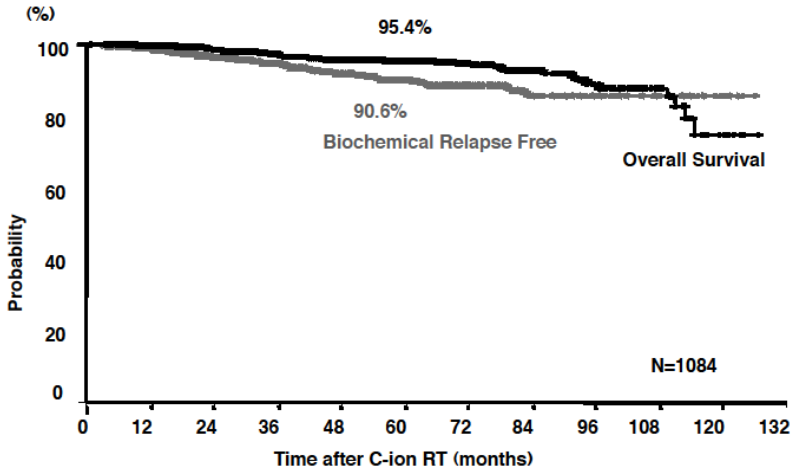

Figure 4. Overall survival and biochemical relapse free rate of patients treated with C-ion RT at NIRS

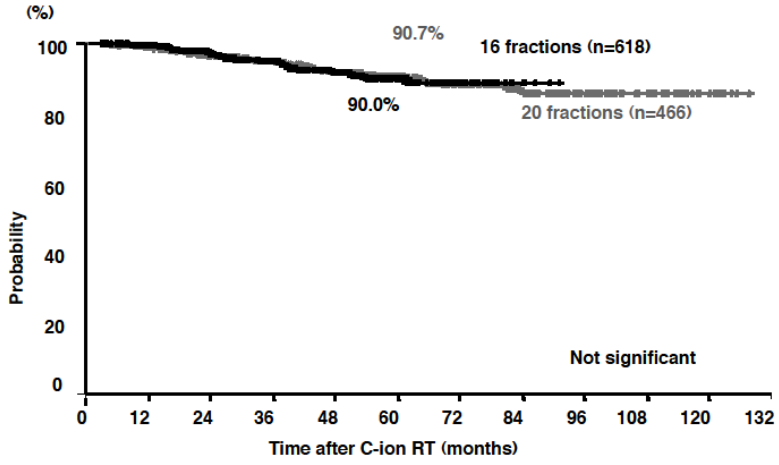

Figure 5. Biochemical relapse free rate by fractionation of C-ion RT

Additional analysis was carried out to evaluate the influence of several prognostic factors on bNED and cause-specific survival rate (CSS; survival rate limited to the prostatic cancer caused death), such as pretreatment serum PSA, GS, clinical stage, and dose fractionation. As a result, initial PSA of more than or equal to 20.0ng/ml

was a significant factor for CSS (p=0.0301) and marginally significant for lower bNED (p=0.0678). Clinical stage of the primary lesion (T-stage) and the centrally reviewed GS also had significant influence on bNED and CSS, that is primary lesion of T3 and GS ≥ 8 was related to poor prognosis (Table 3). However, 5-year bNED of 84.1% in T3 patients and 83.8% in GS ≥ 8 patients were both quite high compared to other radiotherapy series.

Table 3. Biochemical relapse free rate (bNED) and Cause-specific survival rate (CSS) according to risk factors

			5-year rates (%)			
		No.pts.	bNED	p-value	CSS	p-value
All		861	91.0		94.7	
Stage	T1/2	614	94.0	0.0000	100	0.0001
	T3	247	84.1		95.8	
PSA	< 20	595	92.1	0.0678	99.5	0.0301
	20 ≤	266	88.7		97.2	
Gleason score	≤ 6	206	92.3	0.0072	100	0.0110
	7	412	94.3	0.0004	99.2	
	8 ≤	243	83.8		96.6	

Table 4 is a risk grouped comparison of survival rate on large-scale clinical studies of combined therapy of X-ray therapy and endocrine therapy performed in the U.S. and the survival rate on carbon ion radiotherapy. The result shows that the survival rate is higher in the carbon ion radiotherapy in any groups.

Table 4. Comparing Overall Survival Rate of C-ion RT with Results of Meta Analysis of RTOG studies

Studies	Dose (Gy/fr.)	Overall Survival Rate					
		Group 2		Group 3		Group 4	
		No. pts.	5-y OS	No. pts.	5-y OS	No. pts.	5-y OS
RTOG Meta Analysis*							
RT alone	65-70/30-35	443	82%	338	68%	324	52%
RT + Hormone	65-70/30-35	114	76%	138	79%	103	63%
Carbon + Hormone	66-63/20 or 57.6/16	381	99%	321	94%	143	87%

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

4. Discussion

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

As for the treatment morbidity, in the lower urinary tract, the incidence was approximately the same in 63.0GyE/20 fractions carbon ion radiotherapy, intensity modulated radiation therapy and proton, which is

interesting that it shows that this dose has comparable impact against lower urinary tract tissues. While for the 57.6GyE/16 fractions, the lowering of incidence was realized as a real outcome for shortening the treatment term. As for the rectal toxicity, even 63.0GyE showed lower rate than X-ray or proton, this is thought to be the proof of eminent dose convergence of carbon ion beam. In addition, 57.6GyE gained further lowering. Adding shortening to the high dose convergence, significant reduction of toxicity was obtained.

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

5. Conclusion

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

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Carbon Ion Radiotherapy for Liver Cancer

Hiroshi Imada, Shigeo Yasuda, Shigeru Yamada, Makoto Shinoto, Kazuhiko Oonishi, Satoshi Endo, Hiroshi Tsuji, Tadashi Kamada, and Hirohiko Tsujii

Hospital, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
e-mail address: h_imada@nirs.go.jp

Abstract

A trial of carbon ion radiotherapy (C-ion RT) for hepatocellular carcinoma (HCC) was first conducted in April 1995 at the National Institute of Radiological Sciences (NIRS) in Japan. A total of 193 patients with HCC were enrolled in this clinical trial. In the first and second phase I/II clinical trials, dose escalation studies were carried out in incremental steps of 10%, resulting in the confirmation of both the safety and efficacy of short-course regimens of 12, 8, and 4 fractions. Based on the results, a phase II clinical study with fixed fractionation, that is, 52.8 GyE/4 fractions, was performed. A total of 47 patients were treated during this phase II study, which resulted in low toxicity and attained a high local control rate (96%) for 5 years after treatment. The last clinical study was conducted from April 2003 to August 2005, with a more hypofractionated regimen of 2 fractions/2 days, in which 36 patients were safely treated within a dose escalation range from 32.0 GyE to 38.8 GyE. The 2-fraction therapy protocol is continuing under the license of Highly Advanced Medical Technology. There have been no therapy-related deaths and no severe adverse events. We conclude that, because of the low toxicity and high local control rate, C-ion RT is a promising new, radical, and minimally invasive therapeutic option for HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and is the third leading cause of death from cancer (1). Various therapeutic options are presently available for patients with HCC. With regard to radiotherapy, the role for patients with HCC was previously limited and unsatisfactory on the basis of the poor hepatic tolerance to irradiation (2, 3). However, technological advances have made it possible to deliver a higher dose of radiation to focal liver tumors more accurately, reducing the degree of toxicity (4, 5). Carbon ion beams possess a Bragg peak and provide excellent dose distribution to the target volume by specified beam modulations (6-8). They have advantageous biological and physical properties that result in a higher cytocidal effect than that of photons and protons (9-10). Since 1995, carbon ion radiotherapy (C-ion RT) has been performed for the treatment of HCC, and clinical trials were initiated at the National Institute of Radiological Sciences (NIRS) in Japan.

Methods and Materials

1. An outline of carbon ion radiotherapy for HCC: Clinical trials to medical treatment (Table 1)

In the first and second phase I/II clinical trials, dose escalation studies were carried out in incremental steps of 10% in order to identify the optimum dose. In the first of these trials, 24 patients were treated with a 15-fraction regimen at a total dose range of 49.5-79.5 GyE. In the second trial, 86 patients were treated with short-course regimens, at total dose ranges of 54.0-69.6 GyE in 12 fractions, 48.0-52.8 GyE in 8 fractions, and 48.0-52.8 GyE in 4 fractions. Based on the results of these studies, a third protocol was established to implement a phase II clinical trial using a fixed total dose of 52.8 GyE spread over 4 fractions of 13.2 GyE each (11). The fourth

protocol, a phase I/II clinical study, was performed using an even more hypofractionated regimen of 2 fractions/2 days at total dose levels ranging from 32.0 GyE to 38.8 GyE (12). The eligibility criteria common to all four of these protocols were as follows: (a) biopsy-proven HCC (histological diagnosis); (b) no tumor thrombosis of the main trunk of the portal vein; (c) no multiple viable lesions outside the planning target volume; (d) no previous treatment to target tumors by other forms of RT; (e) ECOG performance status of 0–2; (f) no other active cancers; and (g) digestive tract not in contact with the clinical target volume. Most of the subjects enrolled under these protocols had been judged not to be amenable to, or as having had recurrence after, other treatments, or as having no prospect of an adequate treatment effect with any of the existing therapies. Two-fraction therapy is currently ongoing according to the guidelines allowing careful step-wise dose escalations at a 5% increase rate under the license of Highly Advanced Medical Technology.

Table 1. An outline of the use of carbon ion radiotherapy for HCC

Carbon Ion Radiotherapy for HCC

April, 1995～February, 2011 Total n=274

Protocol	Category	Fractionation	Period	Number
9401	Phase I/II study	15f/5w	1995.4～1997.3	24
9603	Phase I/II study	12f/3w	1997.4～2001.3	34
		8f/2w		24
		4f/1w		28
0004	Phase II study	4f/1w	2001.3～2003.3	47
0202	Phase I/II study	2f/2days	2003.4～2005.8	36
0202(2)	Highly Advanced Medical Technology	2f/2days	2006.4～	81

2. Carbon ion radiotherapy

2-1. Preparation for treatment

One or two metal markers (0.5 × 3 mm) made of iridium wire were inserted near the tumor under ultrasound imaging guidance as landmarks for target volume localization. The irradiation fields were established with a three-dimensional therapy plan based on 5-mm-thick CT images. CT planning was performed using the HIPLAN, which was originally developed for 3D treatment planning (13). The clinical target volume was defined according to the shape of the tumor plus a 1.0-1.5-cm margin. The median target volume was 159 ml (range: 37-1466 ml). Double right-angled field geometry was used for irradiation in most patients (double right-angled field: 77%, double oblique field: 7%, 3-field: 14%, 4-field: 2%). The supine or prone position was selected according to the location of the tumor. Respiratory gating was employed in the CT scan planning and irradiation stages to ensure more accurate delivery of the radiation (14).

2-2. Verification of patient position and target volume localization

To accurately reproduce the patient position, a low-temperature thermoplastic sheet and a customized cradle were used. Patients were immobilized on a rotating couch to permit either vertical or horizontal beam irradiation from any angle. To assess the accuracy of patient positioning and target volume localization, orthogonal fluoroscopy and radiography were used immediately prior to each treatment session.

3. Follow-up and evaluation criteria

All patients were assessed according to a predetermined schedule. After C-ion RT, patients were evaluated on the basis of physical examinations and blood tests once a month for the first year, once every 3 months for the following year, and once every 3–6 months thereafter. Contrast-enhanced CT or MRI was performed every 3 months for the first 2 years and every 6 months thereafter. Local control was defined as no sign of regrowth or new tumors in the treatment volume. Local recurrence was defined as failure of local control. The overall survival was measured from the starting date of treatment until the date of death from any cause. Acute and late toxicities were assessed using the National Cancer Institute Common Criteria, version 2.0, and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. In addition, liver toxicity was assessed by the Child-Pugh score, a commonly used marker of hepatic functional reserve in patients with chronic liver disease, on a rating scale from 5 to 15 points, with the score increasing with a deterioration of hepatic function.

Results

A. Protocols 9401, 9603, and 0004 (4-15 fraction regimen C-ion RT for HCC)

The results of the clinical trials up to the 4-fraction regimen for which observations have been continued for 5 years or longer are described below.

1. Toxicities

No therapy-related deaths occurred in the patients treated under any of the three protocols. There was no grade 4 hepatic toxicity. With regard to the Child-Pugh score, the increase in the score associated with C-ion RT remained within 1 point or below in many patients in the early (within 3 months of the start of radiotherapy) and late phases (after 3 months) (Fig. 1). This demonstrated that the changes in liver function remained minor after C-ion RT was initiated. The number of cases reported to have a score increase of 2 points or more in the late phase, which is of particular clinical significance, tended to be smaller with decreasing fraction numbers. No serious adverse effects were noted in the digestive organs.

2. Anti-tumor effects

HCC develops in a successive manner, fostered by the underlying cirrhosis of the liver. Patient survival is therefore determined by the overall results, including the treatment of recurrent lesions and also the treatment of hepatic insufficiency in cases where there is a decline in liver function. As a result, the survival rate does not reflect the efficacy of any particular treatment alone. In comparing the effectiveness of the different therapies for HCC, it is therefore easier to make a judgment on the basis of the local control rate rather than the survival rate. In the present clinical trials, other treatments proved ineffective or led to recurrence in 57% of the patients, and as the phase I/II trials were conducted as dose escalation studies to determine the recommendable dose, there is a possibility that some of the patients may have been treated with a dose that was less than optimal. It is therefore not possible to make a simple comparison of the survival rates achieved in these clinical trials with other treatments.

The local control rates for the analyzed lesions are shown separately according to the protocol and fractionation regimen (Table 2). There were no significant differences in the control rates among the patients treated with the different fractionation schedules.

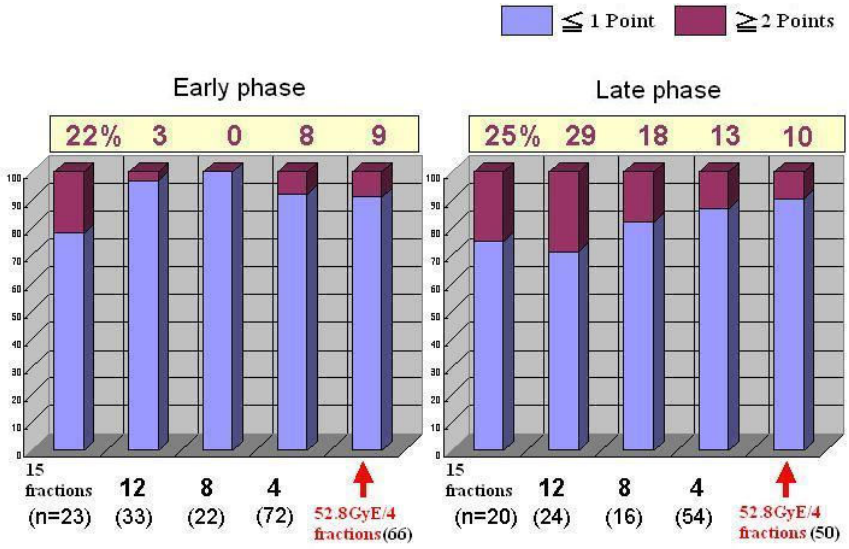


Fig. 1: The changes in the Child-Pugh score before and after C-ion RT

Variations in the Child-Pugh score, an international standard used to assess the degree of hepatic insufficiency before and after irradiation, were studied. The degrees of hepatic insufficiency can be evaluated with the Child-Pugh score on a scale from 5 to 15 points. The score increases as the degree of hepatic insufficiency increases.

The increase in score associated with C-ion RT remained within 1 point or below in many patients in the early (within 3 months of start of radiotherapy) and late phases (after 3 months) after treatment.

Table 2. The results of clinical trials for HCC with C-ion RT

Trial		Phase I/II	Phase I/II			Phase II	52.8GyE/4f
Number of fractions		15	12	8	4	4	4
Total dose (GyE)		49.5-79.5	54.0-69.6	48.0-58.0	48.0-52.8	52.8	52.8
Number of lesions		24	34	24	28	47	69
Maximum tumor diameter (cm)	Median	5.0	3.7	3.1	4.6	3.7	4.0
	Range	2.1-8.5	1.5-7.2	1.2-12.0	2.2-12.0	1.2-7.5	1.2-12.0
Recurrent Tumor	yes	18 (75%)	18 (53%)	16 (67%)	18 (64%)	20 (43%)	35 (51%)
	no	6 (25%)	16 (47%)	8 (33%)	10 (36%)	27 (57%)	34 (49%)
1-year local control (%)		92	97	91	89	96	94
3-year local control (%)		81	86	86	89	96	94
5-year local control (%)		81	86	86	89	96	94

B. Protocol 0202, 0202(2) (2 fractions/2 days)

1. Toxicities

No therapy-related deaths occurred in the hypofractionation trial. There were no cases of grade 4 hepatic toxicity. With regard to the Child-Pugh score, in the late phase (3 months after treatment), an increase of 2 points and more occurred in 5% and 7% in the smaller tumor group (≦5 cm) and the larger tumor group (>5 cm), respectively. There was no significant difference between the two groups (P=0.8424). This demonstrated that the changes in liver function remained minor after C-ion RT was initiated. No serious adverse effects were noted in

the digestive organs.

2. Anti-tumor effects

The local control rates were 94.5% and 90.8% at 1 year, and 94.5% and 73.7% at 3 years in the higher dose group (≧42.8GyE) and the lower dose group (≦40.8GyE), respectively. The patients in the higher dose group showed a better local control rate than those in the lower dose group (P=0.0785). In the higher dose group, the local control rates after both 1 and 3 years were 92.7% in the smaller tumor group (≦5 cm) and 100% in the larger tumor group (>5 cm), respectively.

Discussion

1. Standard therapies for HCC

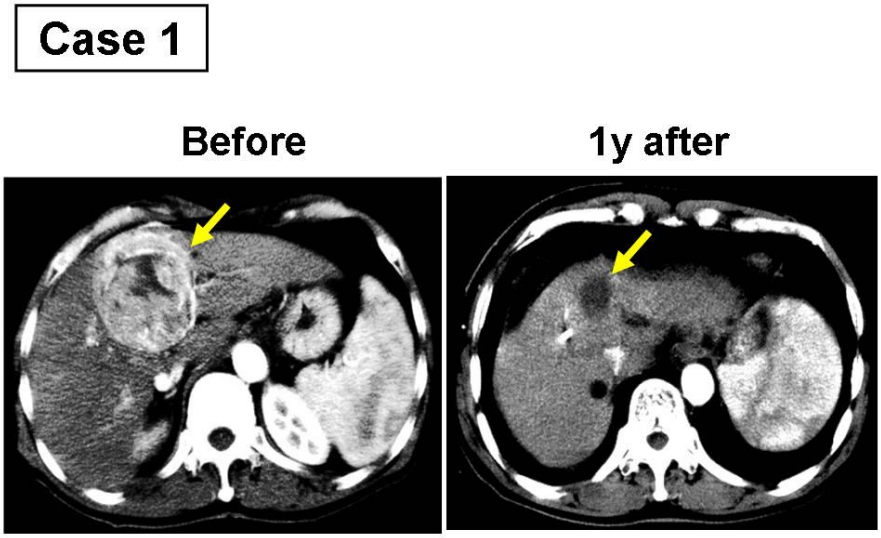
The standard therapies for HCC are hepatectomy, transcatheter arterial embolization (TAE), percutaneous ethanol injection (PEI), radio-frequency ablation (RFA), and liver transplantation. According to the Survey and Follow-up Study of Primary Liver Cancer in Japan, the relative use of these therapies in the treatment records of all patients for the two-year period from January 1, 2004 through December 31, 2005 were: hepatectomy in 32% of case, TAE in 32%, and percutaneous local therapy involving PEI, percutaneous microwave coagulation therapy (PMCT), and RFA in 31%. Each of these procedures has merits and drawbacks. For example, while hepatectomy provides the best certainty of removing cancer cells, the procedure also results in serious stress on both the liver and the body as a whole. TAE is clinically useful and has a relatively low degree of invasiveness, but is of limited radicality. PEI and RFA, on the other hand, are simple procedures offering a high degree of radicality, but their effect is limited to comparatively small tumors (less than 3 cm in diameter). The use of radiotherapy for HCC has been considered difficult in view of the problems associated with radiation-induced hepatic insufficiency (15, 16). However, progress in the development of irradiation devices in recent years has made it possible to achieve highly localized irradiation. This has spurred advances in radiotherapy research for liver cancer (17-22).

2. Optimal candidates for C-ion RT

We have already reported that C-ion RT used for the treatment of HCC is safe and effective, and that it causes only minor liver damage (10). We investigated the reason why liver function is retained, then, non-irradiated lesion of liver is considered to contribute to the retention of liver function (23). For patients with extensive infiltration and those with multiple lesions, it is difficult to achieve radicality with C-ion RT alone. C-ion RT is therefore indicated for patients with a level of liver function corresponding to Child-Pugh grade A or B. For small lesions 3 cm or less, however, other minimally- invasive, effective, and low-cost therapies, such as PEI and RFA, are available. In contrast, lesions larger than 3 cm are difficult to treat with PEI or RFA alone, making them ideal targets for C-ion RT. Moreover, even for lesions less than 3 cm in diameter that are adjacent to the porta hepatis, minimally-invasive treatment without complications is an important issue. We compared the efficacy and toxicity of C-ion RT of 52.8GyE in 4 fractions for patients with HCC in terms of the tumor location (adjacent to the porta hepatis or not) and found that there were no significant differences in liver toxicity. Excellent local control was obtained independent of the tumor location. Therefore, in certain patients with a higher risk of injury to the bile duct when undergoing RFA, C-ion RT appears to offer a promising therapeutic alternative (24).

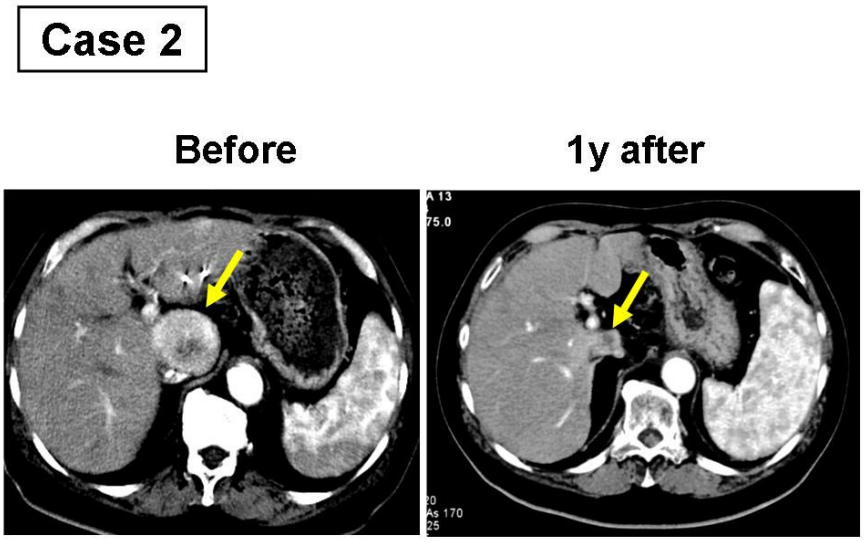
Conclusion

C-ion RT is safe and effective, and it seems to have promise as a new, radical, and minimally invasive therapeutic option for HCC. However, further careful follow-up is still needed to confirm its clinical efficacy in practical medicine.



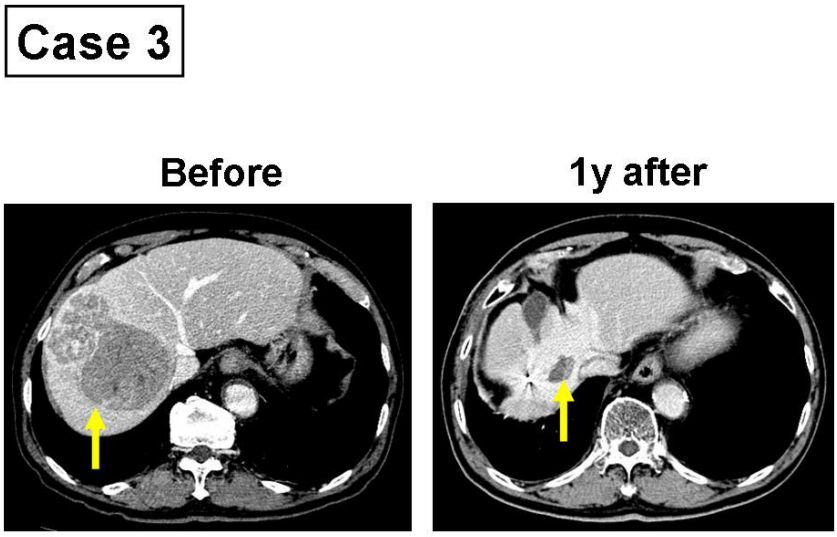
Case 1

A 67-year-old male had a HCC lesion of 7 cm in diameter in segment IV. He survived 5 years after C-ion RT of 72.0 GyE delivered in 15 fractions.



Case 2

A 72-year-old male had a HCC tumor that was 4.6 cm in diameter in segment I. He survived for 7 years after C-ion RT using 52.8 GyE in 4 fractions.



Case 3
A 77-year-old male had a HCC that was 10.5×7.7 cm in the right hepatic lobe. He is still alive 4 years after C-ion RT of 38.8 GyE in 2 fractions.

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Status and Future Plan of HIMAC

Koji Noda, Takashi Fujita, Shigekazu Fukuda, Takuji Furukawa, Taku Inaniwa, Yoshiyuki Iwata, Nobuyuki Kanematsu, Atsushi Kitagawa, Tadafusa Kumagai, Naruhiro Matsufuji, Shinichi Minohara, Manabu Mizota, Kota Mizushima, Shinichiro Mori, Takeshi Murakami, Masayuki Muramatsu, Shinji Sato, Toshiyuki Shirai, Eiichi Takada, Yuka Takei, Shunsuke Yonai

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
Corresponding Author: Koji Noda, e-mail address:noda_k@nirs.go.jp

Abstract

The first clinical trial with carbon beams generated from HIMAC was conducted in June 1994. The total number of patients treated was in excess of 6,100 as of August 2011. The impressive advance of carbon-ion therapy using HIMAC has been supported by high-reliability operation and by the development of both the accelerator and beam-delivery technologies. The status and future plan of HIMAC is described in this report.

1. Introduction

Heavy-ion beams are very suitable for the treatment of deeply seated cancer because of an excellent physical-dose distribution and high-LET characteristics around the Bragg peak. Therefore, NIRS decided to carry out heavy-ion cancer therapy with HIMAC [1]. The first clinical trial of cancer treatment with carbon beam was conducted in June 1994. In the view of the significant growth in the number of protocols, in 2003, the Japanese government approved the carbon-ion radiotherapy (RT) with HIMAC as an advanced medical technology. The total number of patients treated until August 2011 was more than 6,100. The impressive advance of carbon-ion therapy using HIMAC has been supported by high-reliability operation and by the development of both the accelerator beam-delivery technologies. Furthermore, we carried out the design study and the R&D work with HIMAC for a standard carbon-ion RT facility in Japan [2]. As a result, a pilot facility of the standard carbon-ion RT was constructed by Gunma University in cooperating with NIRS and has successfully carried out carbon-ion RT since March 2010. For the further development of the HIMAC treatment, on the other hand, “New Treatment Research Facility Project” [3] has been progressed at NIRS. This report describes the status and future plan of HIMAC.

2. Development of HIMAC Technology

The HIMAC treatment has been carried out with a high reliability, owing to a stable operation of the HIMAC accelerator and beam-delivery systems employing the beam-wobbling and ridge filter method. At present, around 100 irradiations a day at maximum are carried out under one-shift operation, and around 750 patients a year were treated under 180 days operation. On the other hand, the new treatment research facility project has been progressed since 2006, for the further development of the HIMAC treatment. In this project, utilizing the existing HIMAC accelerator, the beams are delivered to the new facility having three treatment rooms. Two of them are equipped with both horizontal and vertical beam-delivery systems and the other one for a rotating gantry, which employ the fast 3D scanning technology. Two treatment-simulation rooms are also equipped for patient positioning as a rehearsal, and for observing any change in the target size and shape during the entire treatment period with an X-ray CT. Furthermore, there are six rooms devoted to patient preparation before irradiation. A schematic view of the HIMAC facility with new treatment research facility and that of the treatment room E are shown in Fig. 1and 2, respectively. At present, the carbon-ion RT with the fast 3D scanning has been carried out since May 2011 in one treatment room (treatment room E) equipped with both horizontal and vertical beam-delivery systems. The second treatment room F is now under construction, while the rotating gantry is in the design and R&D stage.

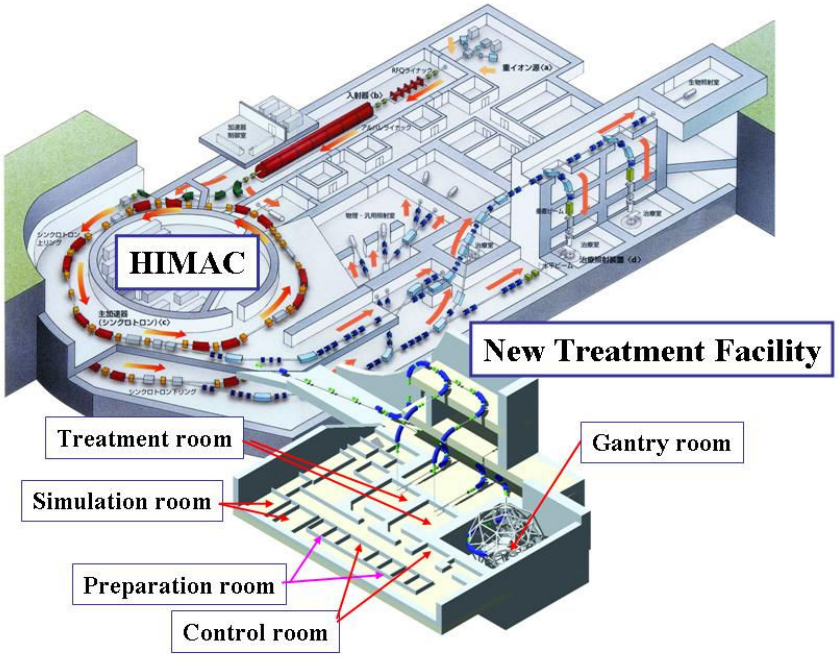

Fig. 1: Schematic view of the HIMAC facility with the new treatment research facility.

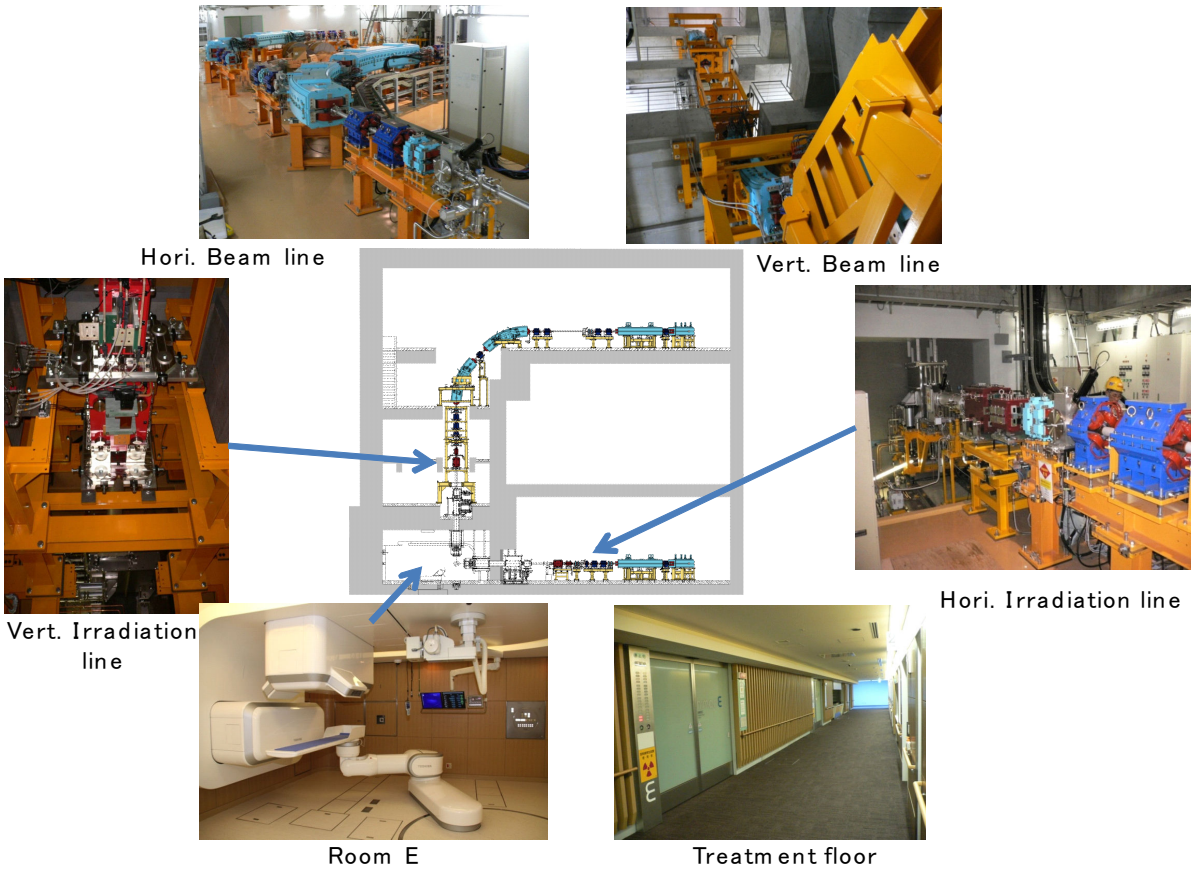

Fig. 2: Schematic view and photos of the horizontal and vertical beam lines to the room E in the new facility. The lower photos show the inside of the room E and the treatment floor in the second basement.

2.1 Development of the HIMAC beam-delivery method

Respiratory-gated irradiation

Damage to normal tissues around tumor was inevitable in treatment of a tumor moving along with respiration of a patient. A respiration-gated irradiation system, therefore, which can respond quickly to irregular respiration, was developed [4]. In this system, the irradiation-gate signal is generated only when target is at the design position and the synchrotron can extract a beam. The beam is delivered by the RF-KO extraction method [5], according to the gate signal. This method has been applied to liver, lung and uterus cancers since February 1996.

Layer-stacking irradiation method

In a conventional irradiation method, the fixed SOBP (Spread-Out Bragg Peak) produced by a ridge filter results in undesirable dosage to the normal tissue in front of target, because the width of an actual target varies within the irradiation field. In order to suppress the undesirable dosage, thus, the layer-stacking irradiation method was proposed [6], and the HIMAC irradiation system has been upgraded to put the technique including the treatment planning [7] into practice.

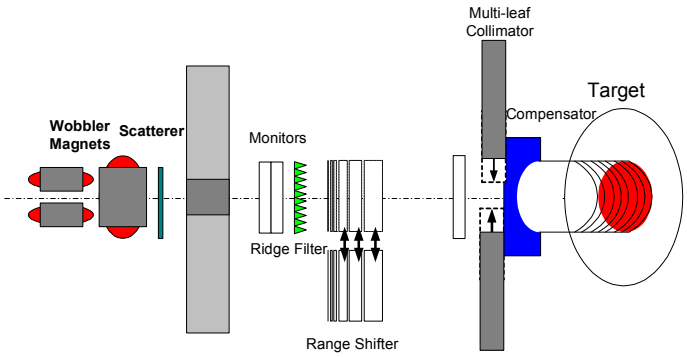

Fig. 3. Schematic drawing of the layer-stacking irradiation method.

3D scanning irradiation method

In order to keep the sophisticated conformations of the dose distributions even in shrinkage of the target size and a change of its shape during the entire treatment, it has been required that treatment planning is carried out just before each fractional irradiation, which we call adaptive cancer therapy. The new treatment research facility should employ a pencil-beam 3D scanning method for a fixed target, a moving target and/or a target near critical organs, toward the target of the implementation of adaptive cancer therapy. For the purpose, we have developed a phase-controlled rescanning (PCR) method [8] with a pencil-beam, especially for treatment of moving target. It was verified by the simulation study that the PCR method can give uniform dose distribution even under irradiation of a moving target. For realizing the PCR method, the following technologies were developed: (1) intensity-modulation technique for a constant irradiation time on each slice having a different cross-section and (2) fast pencil-beam scanning technique for completing several-times rescanning within a tolerable time. After the performance of the PCR was successfully verified [9,10], the fast 3D scanning irradiation port was constructed in the new treatment research facility.

Rotating gantry with 3D scanning

3D pencil-beam scanning with the multi-directions can realize the multi-filed optimization that significantly increases a dose concentration, which will bring a shorter course treatment compared with the present carbon-ion RT. For this purpose, NIRS decided to construct a heavy-ion rotating gantry, which has been approved by the Japanese government. The previous design of the rotating gantry in NIRS using normal conducting magnets [11], as the schematic view is shown in Fig. 4. The size is 15 m in diameter and 17 m in length, and its total weight is about 350 tons. The almost half of the weight is the magnets and the counterweight of the magnets. We have developed the superconducting magnets for the rotating gantry in order to reduce the size and the weight. In the

present design, 8 superconducting magnets are used and the maximum magnetic field is about 3 T, when the maximum beam energy is 430 MeV/n [12]. The gantry radius is 5.5 m and the total length is 13 m. The total weight is less than 200 tons. We expect that the size and weight of the carbon gantry become those of the proton gantry (Fig. 4). The 3D scanning system is identical with that of the fixed port. We have already constructed the test magnets and hope to install the superconducting rotating gantry within a few years.

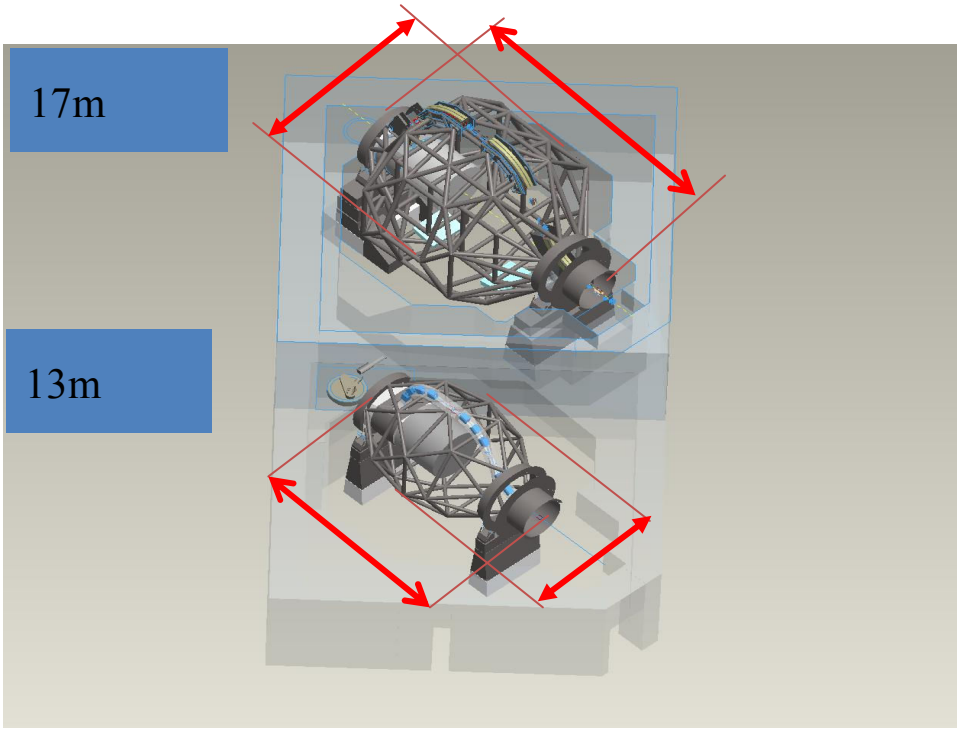

Fig. 4: Schematic views of the normal-conducting (NC) and super-conducting (SC) rotating gantries for carbon beam. The size and weight of the gantry is almost the same as those of the proton one

2.2 Development of the HIMAC accelerator system

RF-KO slow extraction method

We developed the RF-KO slow extraction method for a respiration-gated irradiation system using the broad-beam irradiation (wobbler) method. This method has a huge spill ripple due to the coherency in its extraction mechanism. However, the huge spill ripple has never disturbed the dose distribution in the wobbler method, because the ripple frequency of around 1 kHz is much different from the wobbling one of around 60 Hz. In the beam-scanning method, on the other hand, the huge spill ripple affects the lateral dose distribution. As a result of study, we proposed the dual FM method and the separated function method [13], which were already verified by the experiment and has been routinely utilized. Further, the intensity modulation of the extracted beam is an essential feature of the PCR method. Thus we have also developed the global-spill (Hz-order) control method [14]. Since this control method can predict the extra-dose occurred when the beam moves between raster points, the scanning speed can be increased by five times compared with the conventional one [15].

Intensity upgrade and extended flat-top operation

For efficient operation of the 3D scanning, the beam intensity extracted from the synchrotron has been increased in order to complete single-fractional irradiation with one operation cycle. In this case, the efficiency of the gated irradiation will be increased, because we can extend the flattop infinitely in principle. As a result, the extended flattop operation will save considerably irradiation time. In order to increase the beam intensity, we have thus carried out a tune survey during beam injection. As a result, it was found that the 3rd-order coupling resonance caused beam loss. This resonance was corrected by four sextupole magnets, and the beam lifetime in

the injection-energy level was increased by more than 5 times. In addition, we tried multi-harmonics operation of the RF acceleration system in order to suppress the space-charge effect after bunching. This operation increased the acceleration efficiency by around 40%. Consequently, around 2×10^{10} carbon ions can be accelerated to the final energy. This intensity is sufficiently high to complete single-fractional irradiation for almost all tumors treated with HIMAC when using the 3D-scanning method with beam-utilization efficiency more than 90%. The extended flattop operation was successfully tested at the HIMAC synchrotron, and the stability of the beam-profile was investigated. The horizontal and vertical beam profiles during extraction duration of 100 s were measured by a multi-wire proportional counter. As a result of an analysis of the measurement, it was estimated that both the position and the size duration of 100 s were stabilized within ±0.5 mm at the iso-center.

Variable energy operation

Even in the broad-beam irradiation method, quick energy change is useful for an efficient operation. In the pencil-beam 3D scanning, variable energy operation by accelerator itself has great advantages over the range shifter method: keeping the spot size small and suppressing secondary neutron production. GSI developed the variable energy operation in cycle-by-cycle. In this case, it takes a few second of the operation cycle to change the energy for one slice change in the scanning method. Hitachi also developed the similar variable energy operation of the synchrotron for proton RT. NIRS is under developing the variable energy operation within one operation cycle of the HIMAC synchrotron. In the NIRS method, the energy of the extracted ion can be changed by step-wised energy pattern at the flattop of synchrotron operation. The duration of the flattop can be arbitrarily determined by a clock on/off in the flattop period, as shown in Fig. 5. As the first step, an eleven-step energy operation was developed. This operation has been routinely utilized for the treatment by the fast 3D scanning, although the beam energy is fixed during the one fractional irradiation because a part of transport line consisted of some block-iron magnets. As the second step, the 147-step energy pattern, which can change the energy ranging from 430 to 80 MeV/n, has been developed. The energy change in one step corresponds to a range shift of 2 mm, and it will take less than 100 ms to change a slice [16]. A beam commissioning for the variable energy operation will start after the block-iron magnets in a part of transport line from the synchrotron to the new treatment research facility will be replaced to laminated-iron magnets.

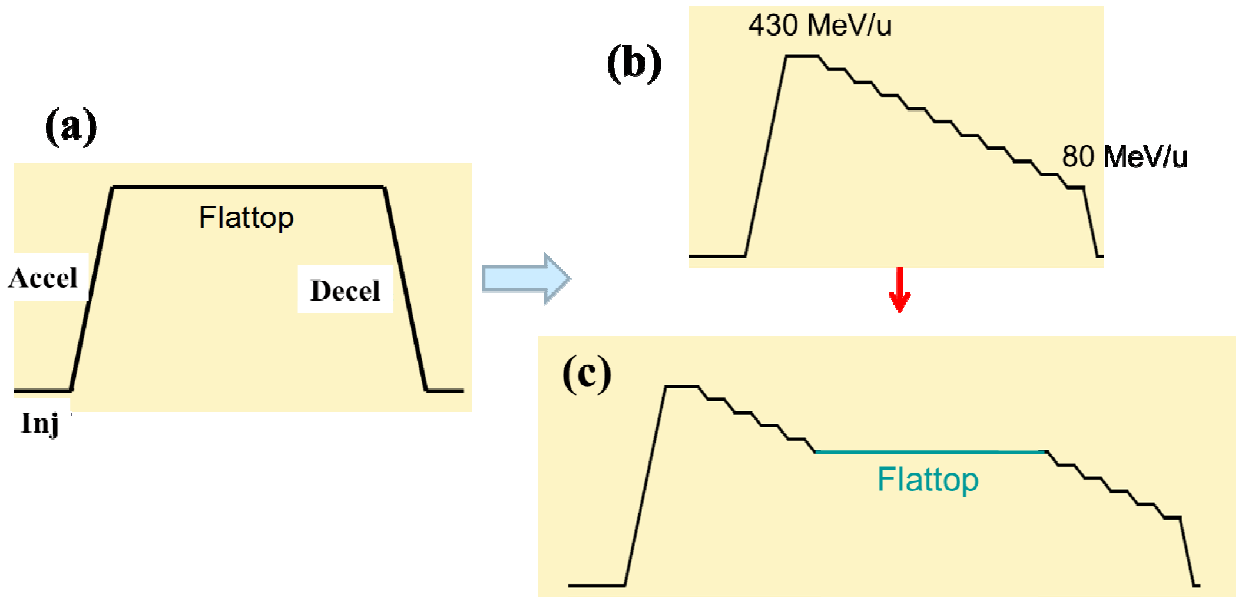

Fig. 5: Schematic diagram of variable energy operation at HIMAC. (a) Conventional operation pattern, (b) Variable energy operation pattern and (c) Extended flattop with arbitrary energy by the clock on/off.

4. Summary

Figure 6 shows the development flow of the heavy-ion cancer radiotherapy facility in Japan. Carbon-ion radiotherapy with HIMAC has treated more than 6, 100 pts since 1994. In these treatments, the new technologies such as the respiratory-gated irradiation and layer stacking irradiation methods, developed by NIRS, has applied to the cancer therapy with HIMAC. On the basis of the clinical study and the related technologies developed by NIRS, the downsized carbon-ion radiotherapy facility was developed and its pilot facility was constructed by Gunma University in cooperation with NIRS. The pilot facility has been initiated since March 2010. The new treatment research project, based on the fast 3D scanning technology, has carried out treatments since May 2011. One has expected the further developments of heavy-ion radiotherapy using a pilot facility in Gunma University and the new treatment research facility in NIRS, and these technologies will play an important role to heavy-ion cancer radiotherapy in the world.

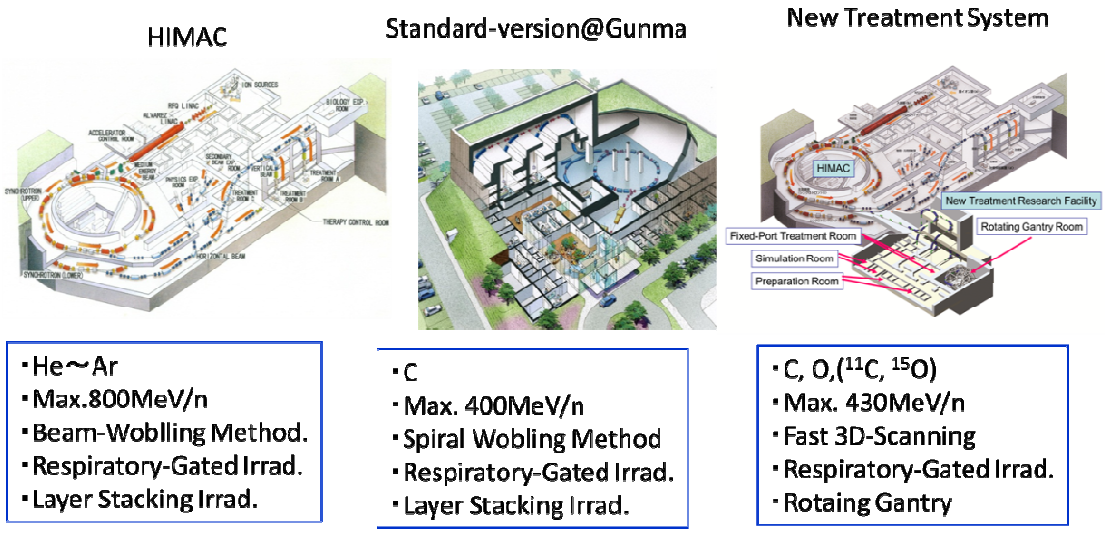

Fig. 6: Development flow on heavy-ion cancer radiotherapy technologies.

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Multi-dimensional Image Guided Carbon Ion Radiotherapy

Shinichiro Mori, PhD , Motoki Kumagai, PhD, Yuka, Matsuzaki, PhD, Taku Inaniwa, PhD,
Takuji Furukawa, PhD, Yuka Takei, Toshiyuki Shirai, PhD, Takeshi Murakami, PhD, Koji Noda, PhD.

Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
Corresponding Author: Shinichiro Mori, e-mail address: shinshin@nirs.go.jp

Abstract

Purpose: Organ movement due to respiration may change the run of a charged particle beam that can result in degradation of dose conformation to the target. We introduced our approaches to quantitatively assessing potential problems in treatment planning due to organ movement by using four-dimensional images.

Methods and Materials: Several tens of inpatients with lung, pancreas or liver cancer underwent 4DCT acquisition under free breathing conditions. For lung cancer cases, fluoroscopic images were acquired after 4DCT images. The patient respiratory signal was obtained by an external respiratory sensing monitor. For the 4DCT study, gross tumor volume (GTV) and normal tissues were contoured on the CT data set and the intrafractional motion was calculated. For the DFPD study, target motion was calculated by marker-less template matching and compared with the external respiratory signal.

Results: 4DCT images obtained improved the evaluation of tumor displacement without 4DCT artifacts that were observed using the conventional MSCT. The images were of sufficient quality to calculate particle dose distribution for scanning irradiation for target movement. The correlation between the external and internal intrafractional motions were slightly degraded.

Conclusions: It is necessary to capture intrafractional motion in both treatment planning and irradiation stages. By doing this, we can provide increased treatment accuracy.

Introduction

Worldwide, more than 28 particle treatment centers were operating in 2008, including three carbon ion beam centers, and the construction of new centers is set to continue. Compared with photon beams, charged particle beams provide superior dose conformation, and minimization of excessive dosing to normal tissues. These strengths are due to the characteristic increase in energy deposition of particle beams with penetration depth (proton and carbon ion beams) up to a sharp maximum at the end of the range (Bragg peak).

Organ motion due to respiration has been investigated using a variety of methods, including fluoroscopy, ultrasound (US), MRI, CT and PET, in the lung, liver, pancreas, kidney, and prostate sites. An understanding of motion characteristics in radiotherapy planning is useful for determining internal margins and optimizing beam parameters (beam angle, etc.), because the degradation of image quality due to respiratory motion affects radiotherapy planning and delivery of the treatment beam. We used fast rotating cone-beam CT, which employs approximately 13-cm wide cylindrical 2D detector system built into the frame of a conventional 16 multi-slice CT (Aquilion, Toshiba Medical Systems)(1), to evaluate organ motion. Within this scan range, the 4DCT obtains volumetric cine CT data without resorting to the respiratory phase. Motion artifacts due to breathing were frozen by a temporal resolution of 250 ms, allowing the tumor shape to be evaluated accurately. Moreover, thinner slice thickness and a shorter total acquisition time helped determine target margins without 4DCT artifacts. Organ movement due to respiration may change the run of a charged particle beam that can result in degradation of

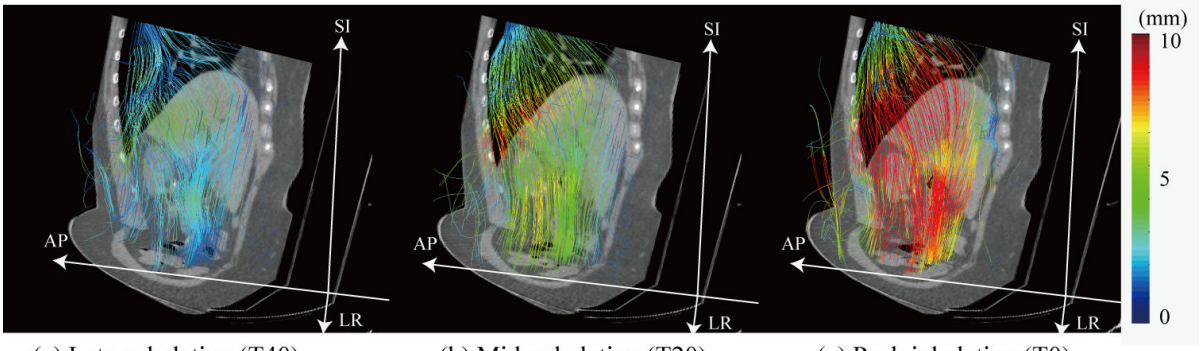
dose conformation to the target. Moreover, treatment planning accounts for organ motion to avoid dose variation. Therefore, although the treatment beam sometimes misses due to movement of the target, better imaging will allow for better treatment accuracy. We herein introduce our approaches to capture images of a moving target and quantitatively assessing the potential problems in treatment planning due to organ movement.

Organ/target motion

We quantified organ and target motion due to respiration in the pancreas, liver and lung sites as a function of time using the 4DCT and DFPD. In the NIRS, patients receiving thoracic and abdominal treatments undergo carbon ion beam treatment with a custom-made immobilization device to improve patient positional reproducibility throughout the treatment course. To more accurately simulate typical clinical conditions, the same immobilization techniques were used during this study.

Geometrical variation was greater around the pancreas tail than the pancreas body and head regions. The average pancreas head, body and tail displacement in the inferior direction for the ungated phase was 8.3 mm, 9.6 mm and 13.4 mm, respectively, which was minimized in the gated phase to 2.8 mm, 2.8 mm and 3.6 mm, respectively. For all six patients with pancreatic cancer, the average pancreas COM displacement relative to that at peak exhalation was mainly in the inferior direction, at 9.6 mm for the ungated phase and 2.3 mm for the gated phase (2).

With regard to the liver site (irradiation administered with patients in the prone position), after the 1st 4DCT were done, the patient couch was moved to the adjacent position to cover the entire liver. As a result, an approximately 25cm longitudinal scan range could be acquired. Geometrical changes due to respiration were quantified by a deformable registration between the reference and respective respiratory phases. The magnitude of the intrafractional displacement was increased close to the inhalation phase, with both AP and SI movement around the diaphragm. However, around the middle abdominal region, the movement was almost SI. Another visualization technique is the intrafractional motion curve shown in Figure 1. These visualizations were useful to understand the rich information provided in the 4DCT, and were useful for optimizing treatment planning. The GTV-COM displacement average in 10 patients was 0.3mm (max: 1.8mm) in the left side, 2.2mm (max: 5.3mm) in the right side, 4.6mm (max: 10.8mm) in the anterior side, 0.1mm (max: 0.3 mm) in the posterior side, and 11.6 mm (max: 17.4mm) in the inferior side. No displacement was observed on the superior side.



(a) Late exhalation (T40) (b) Mid-exhalation (T20) (c) Peak inhalation (T0)

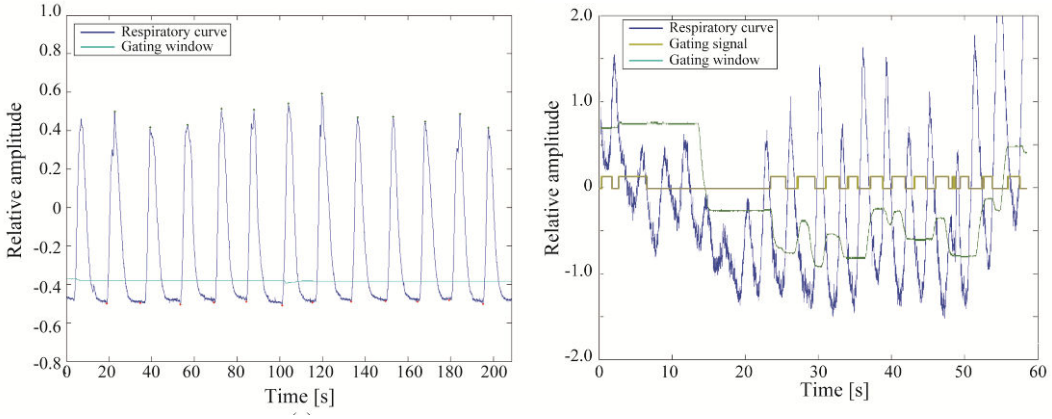
Figure 1. Intrafractional motion curves overlaid on the CT images in oblique view. These curves represent the magnitude of displacement and motion direction from peak exhalation (T50) to respective phases (Tn).

A total of 14 lung cancer patients participated in the 4DCT immobilization study (supine position only). Volumetric cine imaging of the lungs showed continuous movement of the tumor in the axial and sagittal sections. The average GTV-COM displacement relative to that at peak exhalation was 1.4 mm (range 0.5-2.3

mm) in the left-right, 2.2 mm (range 0.8-4.7 mm) in the anterior-posterior, and 6.6 mm (range 1.6-21.8 mm) in the superior-inferior direction.

Some limitations to irradiating a moving target warrant further discussion. While tumor movement as a result of respiratory motion is now well understood, little attention has been paid to movement due to bowel gas movement. Gas bubble movement is due to two physiological processes, respiration and peristalsis. Since the charged particle beam stopping position is strongly dependent on the radiological pathlength from the patient surface, replacing dense tissue with a low-density material such as bowel gas changes the radiological pathlength significantly, resulting in a perturbation in the beam stopping position from that originally planned. Quantitative analysis of dose variation due to bowel gas movement in the treatment course is a more challenging task in charged particle therapy than photon therapy.

Although the human respiratory cycle is not strictly regular, and generally varies in amplitude and period from one cycle to the next, for this study we assumed that the patient respiratory cycle, pattern and tumor position were reproducible throughout the course of treatment. Current treatment planning uses a single respiratory cycle only because the inclusion of respiratory patterns during irradiation cannot be accounted for. Respiratory pattern variations can be considered in treatment planning via the acquisition of 4DCT data for multiple respiratory cycles before treatment, although consideration needs to be given to the very high patient dose this entails. Several approaches to this problem are available. The first is to include respiratory pattern variations in treatment planning via the use of margins, etc. The second is real-time monitoring of target position using either an external marker or internal monitoring system. Owing to the imperfect reproducibility of the respiratory cycle, this relatively extended treatment period may result in inconsistencies between respiratory phase as determined using an external marker on the diaphragm and the movement of the internal anatomy. Thanks to its high temporal resolution and reproducibility of setup position, fluoroscopy is currently the better choice.



(a) (b)

Figure 2. Respiratory signal obtained using an external respiratory sensing monitor (blue line) and gating threshold (light green). (a) Regular breathing pattern. (b) Irregular breathing pattern.

Real time tracking

However, although external systems facilitate the measurement of patient surface position as a function of time, and are in fact in routine use at several treatment centers, they do not provide internal target position. Rather, this can be obtained using 4DCT data and the respiratory signal during 4DCT acquisition. Owing to the imperfect reproducibility of the respiratory cycle, this relatively extended treatment period may result in inconsistencies between respiratory phase as determined using an external marker on the diaphragm and the movement of the internal anatomy. The problem, however, is that neither provides insights into how variable patients' breathing is during the few minutes of treatment. Current 4DCT scans acquire only a single respiratory

cycle, so that, as a result, the patient's respiratory cycle and tumor position are not reproducible for all respiratory activity during treatment. Fluoroscopic images using DFPD were acquired for lung cancer patients from a 45 degree oblique view. To minimize the skin dose, 6 s fluoroscopy with 15fps was repeated 8 times with an acquisition interval time of 12s, thus resulting in a total image acquisition time and study time of 48 s and 180s, respectively (Figure 3). Respiratory signals were obtained by an external respiratory sensing system. The target position was captured by using a multi-template matching method as follows: First, ten template images were binned using the first respiratory cycle images (= 90 images). A bonding box sufficient to cover the target region was set on the template images. The target positions in the respective phase were calculated by using template images. The gating threshold was defined as 20% of the amplitude of the reference cycle (fist respiratory cycle) and the external respiratory signal is shown in Figure 3.

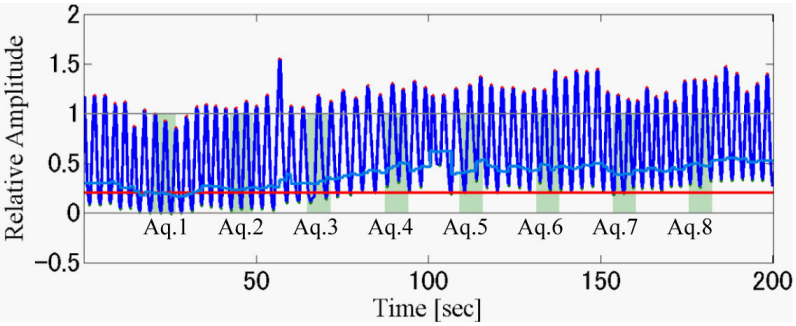


Figure 3. Respiratory signal obtained by the external respiratory sensing monitor (blue line). Red and light blue lines show the 20% gating threshold of the reference respiratory cycle and that of respective cycles. The green square region shows the DFPD image acquisition time. Red and light blue lines were gating threshold of 20% amplitude defined in a referenced cycle and for each cycle, respectively.

DFPD images with the calculated bonding box are shown in Figure 4. The tumor was small, and not clearly observed on the images. Tumor displacement was almost entirely in the SI direction. Quantitative results in SI and AP displacement are summarized in Figure . With regard to SI motion, the external respiratory signal and internal target position were well correlated in the 1st DFPD acquisition. These correlations, however, were degraded after 3rd acquisition. For AP motion, the external and internal correlation was not good for any of thel DFPD acquisition series, and the internal tumor position fluctuated because the tumor was close to the left atrium. As a result, the tumor position was also affected by the patient's heartbeat. In this patient, the SI motion determined by 4DCT was approximately 7 mm in a single respiratory cycle, however, that obtained by fluoroscopy was 17.5mm during a 180 s study time.

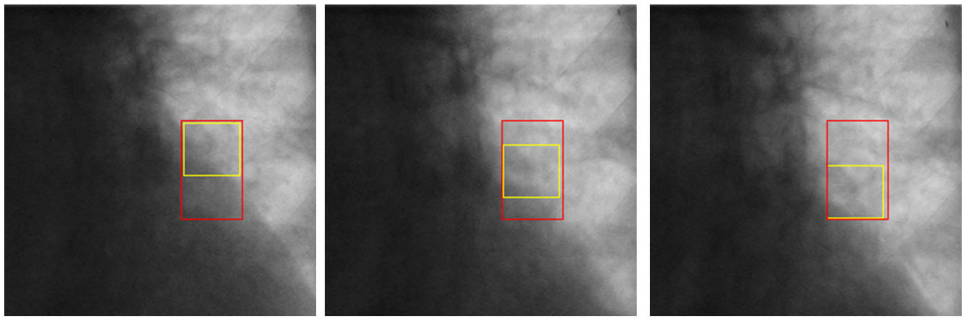
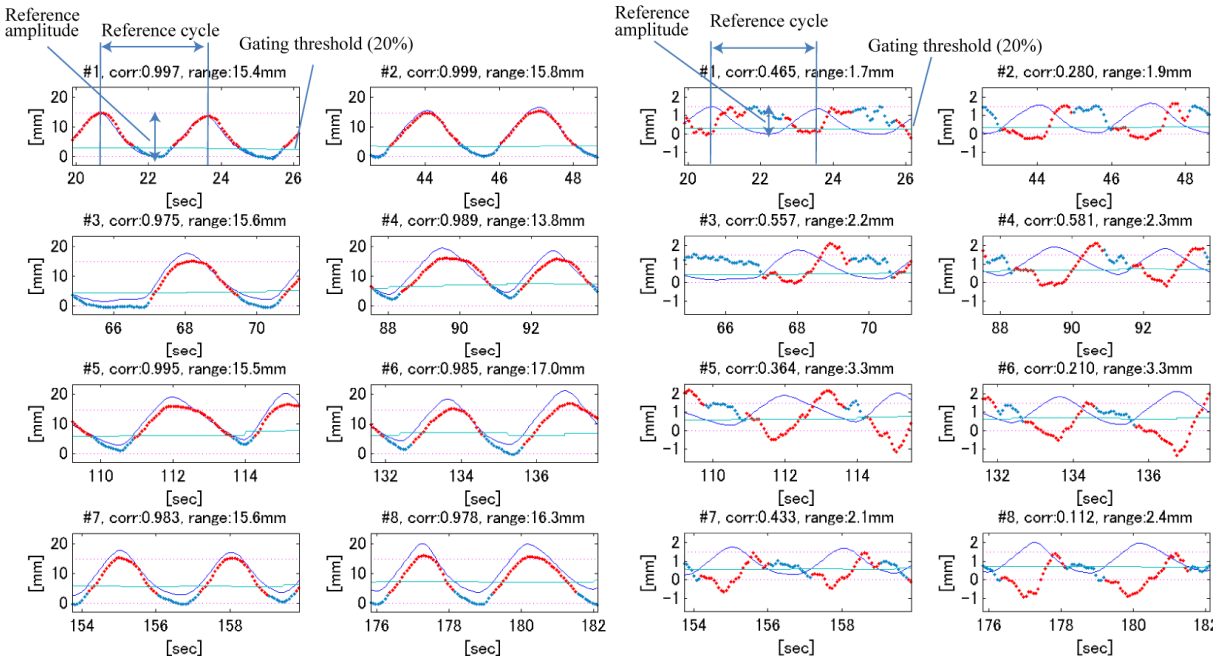


Figure 4. DFPD lung image as a function of respiratory phase. The yellow and red squares show the calculation region and the bounding box of calculation regions.

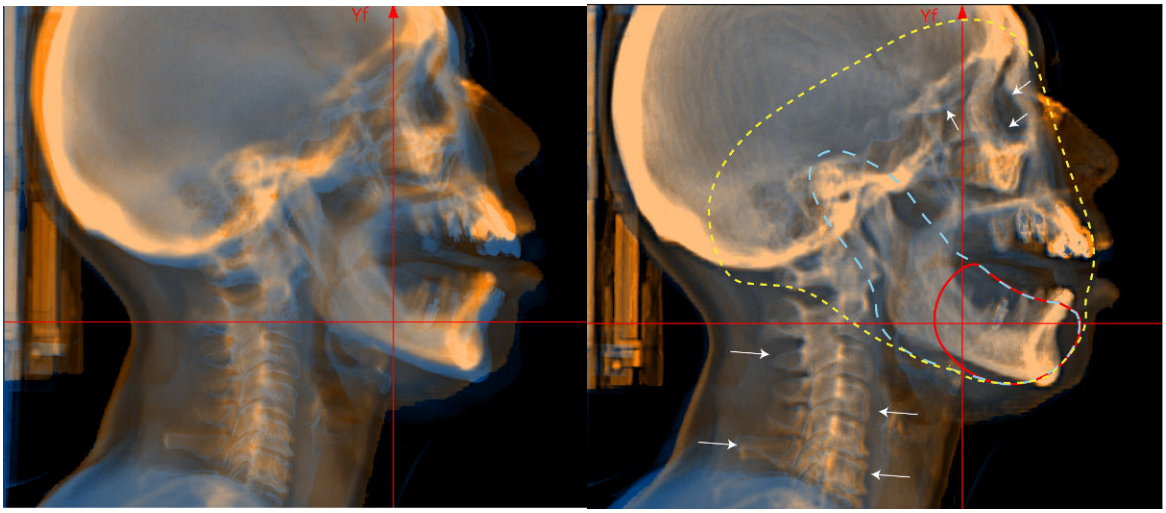


(a) SI motion (b) AP motion

Figure 5. The relationship between external respiratory signal (solid blue line) and tumor displacement obtained by DFPD images (dotted red/blue lines). (a) SI motion. (b) AP motion. The light blue solid line shows the gating threshold (20% of the external respiratory signal in each cycle). The tumor position during the gating window is shown by a dotted blue line.

Patient positional verification

Conventional patient positioning (patient setup) is commonly performed by use of a tattoo on the patient's skin for correct setup of the patient. Recently, several treatment centers have started using a laser marker on the treatment room wall or on the x-ray imaging system. However, patient positioning takes several minutes to complete, and adjustment of the rotational component of the coordinate transformation (yaw, pitch, roll) is more difficult than that for coordinate transformation (left-right, anterior-posterior, and superior-inferior). A more recently introduced patient positional system uses the 2D-3D image registration technique with a combination of 2D imaging, such as portal images, and volumetric CT data used for treatment planning, and it calculates patient positioning errors between the treatment and planning stages. Current CPUs have four or fewer cores in a single integrated circuit, limiting the performance of multithreading computation. An alternative approach, however, is to use a GPU (graphic processing unit) as a parallel computational architecture in place of the CPU. We were able to improve the patient positioning system by including a GPU-based auto-registration function programmed in C++ and CUDA (NVIDIA Corporation, CA, USA). The GPU-based version (NVIDIA TESLA C2050 board (NVIDIA Corporation, CA, USA) gives a 50-fold faster calculation time than the CPU-based software program (2.0 GHz single quad-core CPU Intel Xeon processor, 4 GB physical memory)(3). As a result, auto registration could be finished in less than 30s, with 0.3 mm and 0.2deg geometrical accuracy (Figure 6). This shorter calculation time can help decrease patient positional changes during the setup procedure. Moreover, the high geometrical accuracy could improve dose conformation to the target.



(a) (b)

Figure 6. FPD images (blue layer) overlaid on DRR images (orange layer) (a) before registration and (b) after registration. White arrows marked in lower panels are positional errors which differ from the referenced DRR images. Yellow and blue dotted lines and the reference solid line show large, middle and small ROI regions. Registration parameters were a computation gird of 2 mm, CT slice thickness of 2 mm, middle ROI, and image processing on.

Treatment workflow

Our center recently constructed a new treatment facility for carbon-ion beam scanning treatment as an extension of the existing treatment building (HIMAC: Heavy Ion Medical Accelerator in Chiba), which provides passive beam irradiation. The new treatment facility is designed to facilitate the integration of several devices with the overall goal of increasing treatment accuracy and improving treatment workflow in terms of their physical, technical and clinical aspects (Figure 7). Construction was started in February 2009 and completed in March 2010. Installation of treatment equipment was started in June 2010 and commissioning was completed in March 2011. The Tohoku earthquake (magnitude 9.0 M_w), one of the five most powerful earthquakes recorded since 1900, hit Japan on 11th March 2011, delaying the start of treatment until May 2011. The new facility is organized into three main systems, a Scanning Irradiation System (S-IR), a Treatment Planning System (TPS), and a Patient Handling System (PTH). The PTH covers a wide range of functions, including imaging, geometrical/position accuracy including motion management, layout of the treatment room, and treatment workflow. Because currently available software does not always handle workflow events flexibly, we focused on designing the treatment workflow to be suitable for use with any treatment situation, such as cancelation during irradiation or actual simulation etc., and the restarting of treatment processes.

(a) (b)

Figure 7 (a) Simulation room. (b) Treatment room

Conclusions

We introduced the NIRS approaches to a image guided particle study. It is necessary to capture intrafractional motion in both treatment planning and irradiation stages in order to provide better treatment accuracy. We are presently constructing a new treatment facility which will allow the provision of raster-scanning irradiation, including thoracic and abdominal regions (4). We are convinced, however, that our approach to moving targets in charged particle therapy will be a decisive factor in overcoming problems with treatment accuracy, and will be useful for improving treatment using the scanning irradiation method.

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[3] Mori S, Kobayashi M, Kumagai M, *et al.* Development of a GPU-based multithreaded software application to calculate digitally reconstructed radiographs for radiotherapy. *Radiol Phys Technol* 2009;2:40-45.

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Radiation Emergency Medicine

Overview of TEPCO Fukushima Daiichi NPP accident

Hideo Tatsuzaki,M.D., Ph.D.

Research Center for Radiation Emergency Medicine,
National Institute of Radiological Sciences,
Japan

ICRM,
Riyadh, Saudi Arabia,
27 February – 1 March 2012

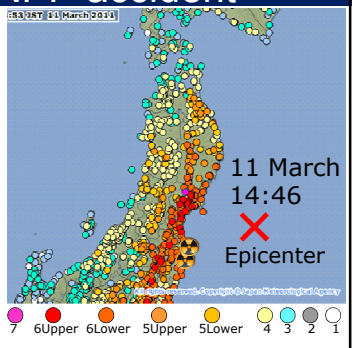
Time-line of TEPCO Fukushima Daiichi NPP accident

11 March 14:46;

- the 2011 Off the Pacific Coast of Tohoku Earthquake
- All AC power supply was lost at Units 1-5 due to Tsunami etc.
- Declaration of Nuclear Emergency

12-15 March:

- Hidrogen explosion at Units 1-3-4 and supression chamber explosin at Unit 2.
- INES level 7 (12 April 2011)
- Release to atmosphere
- Resulted in Combined disaster



Hidrogen explosion of unit 3

Earthquake and Tsunami

- "the 2011 Off the Pacific Coast of Tohoku Earthquake" officially called by JMA.
- from 14:46 JST on 11 March 2011
- Richter scale 9.0
  - the largest one recorded in Japan
- JMA Seismic Intensity: maximum 7
  at Kurihara City, Miyagi Prefecture.
- Aftershocks including six stronger ones magnitute 7≤.

- Victims
  - death toll 15,815,
  - missing 3,966,
  - injured 5,940.
    - National Police Agency: Press release of 30 September 2011.

NPP accident

- TEPCO Fukushima Dai-ichi Nuclear Power Plant
- State of nuclear emergency declared (11 Mar)
- Tsunami damaged the cooling systems, although the reactors at the NPPs automatically had shut down after the earthquake.
- All AC power supply was lost at Units 1-5 due to the earthquake and tsunami.
- Led to
  - a hydrogen explosion of the Unit 1 on 12 March,
  - a hydrogen explosion of the Unit 3 on 14 March
  - explosions of Units (2 and) 4 on 15 March.
- Core melting happened.

Release of radioactive materials

- Release to atmosphere
  - I-131 1.6×10^{17} Bq
  - Cs-134 1.8×10^{16} Bq
  - Cs-137 1.5×10^{16} Bq
    - By NISA 2011-6-6 press release

- Marine (Water leaked into the sea with RI)
  - Water with a large amount of RI (emitting over 1 Sv/h at 10 cm) in pit of power cables poured into the sea between 2-6 April.
    - main cause of contamination of the seawater.
    - Discharge by this event : estimated approx. 4.7×10^{15} Bq
      - Report of Japanese Government to the IAEA Ministerial Conference on Nuclear Safety. June, 2011.
  - Resulted in contaminated fisheries.

(from TEPCO press release 2012.12.27)

Exposed dose to emergency workers at 1F NPP

No Acute Radiation Syndrome

External exposure

Dose(mSv)	Mar	Apr
250<	0	0
200~250	0	0
150~200	9	0
100~150	28	0
50~100	163	25
≤50	3545	5727
total (person)	3745	5752
max(mSv)	199	85
ave(mSv)	14	1.1

External+internal exposure

Dose(mSv)	Mar~Nov
250<	6
200~250	3
150~200	23
100~150	139
50~100	686
≤50	17989
total (person)	18846
max(mSv)	679
ave(mSv)	12

Wide area monitoring
in caution area and evacuation prepared area

- Date：2011. 7. 4～8. 20
- Mesured points：2km mesh-~20points each
- Ambient dose rate (height 1m & 1cm)
- Operator: CRIEPI, TEPCO
- Caution area: Max(1m/1cm) 139.0/368.0μSv/h
- Evacuation prepared area: Max(1m/1cm) 41.3/105.0μSv/h

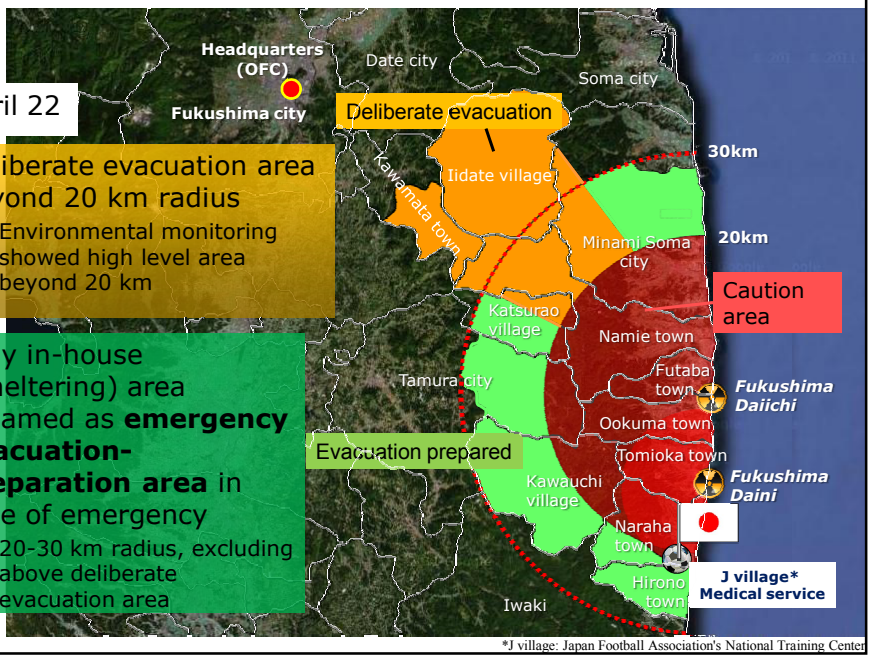
(2011-Sep-1 from cabinet and MEXT)

Evacuation & Sheltering

- **21:23, March11: evacuation of residents within 3km radius from Unit 1 of Fukushima I NPP**
- **5:44, March 12: evacuation within 10km radius from Fukushima I NPP**
- **17:39, March 12: evacuation within 10 km radius from Fukushima II NPP**
- **18:25, March 12: evacuation within 20 km radius from Fukushima I NPP**
- **March 15: in-house stay was directed for the residents from 20 to 30 km radius from Fukushima I NPP**
- **March 25: Chief Cabinet Secretary, Mr. Edano promoted voluntary evacuations for the residents within the area from 20 km to 30 km from Fukushima I NPP**

Evacuation area

- April 22
- Deliberate evacuation area beyond 20 km radius
  - Environmental monitoring showed high level area beyond 20 km
- Stay in-house (Sheltering) area renamed as **emergency evacuation-preparation area** in case of emergency
  - 20-30 km radius, excluding above deliberate evacuation area



Special system

- Combined disaster damaged some emergency systems such as ERSS, SPEEDI, or monitoring posts
- ERSS (Emergency Response Support System)
  - Monitor status of reactors and forecast progress of accident
  - Could not be utilized due to no plant information
- SPEEDI (System for Prediction of Environmental Emergency Dose Information)
  - Quantitative forcast of atmospheric concentrations RI and dose rates
  - Could not be unitized no source term info.
- Alternative usage ->
  operaton porcess and disclosure of results: problem
- Most of monitoring posts: dysfunctional

Evaluation of exposure

- Fukushima Prefecture determined screening level
  - decontamination the whole body at 100 kcpm
  - partial decontamination at 13 kcpm
- More than 190,000 people were checked (as of 23 May)
  - most of them were under the 100 kcpm .
- More than 1000 children between 0-15 years old were surveyed on thyroid exposure
  from 26-30 March.
  >no children exceeding the screening level.
- Whole body counters - on-going as of 31 Dec. 2012.

Internal exposure test for residents with WBC (Fukushima prefecture)

- Date:27 Jun-31 Dec
- Subject:preliminary test for health survey; resident of Kawamata-cho, Namie-cho, Iidate-mura
- Examination: JAERI,NIRS
- Total 11,816 persons

Committed effective dose (mSv)	Number of people
<1	11,792
1	12
2	10
3	2
total	11,816

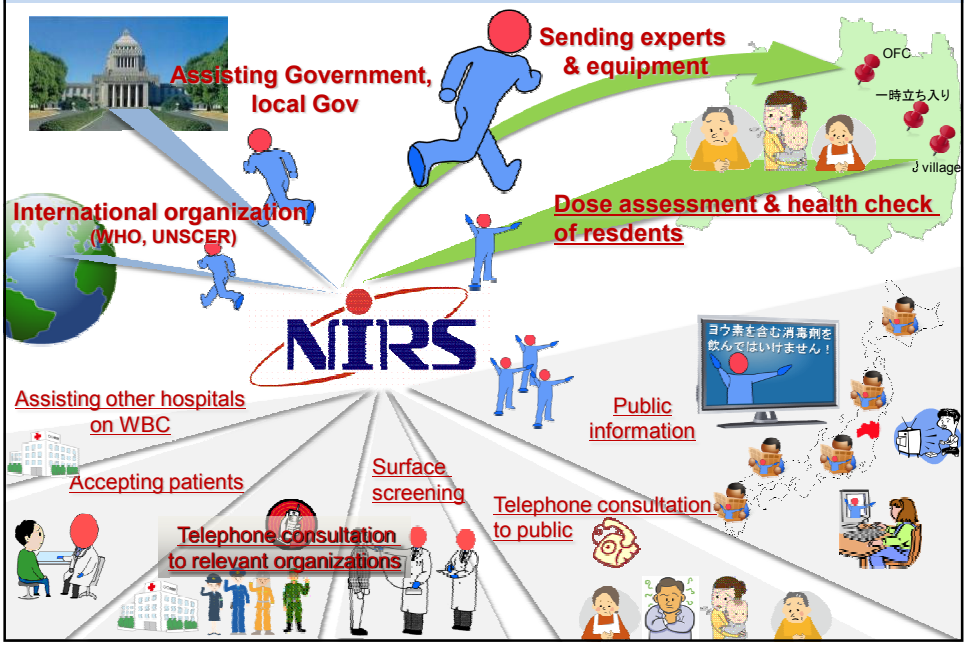
(from home page of Fukushima Pref. released on 2012.1.25)

RI in foodstuffs
(total number from Mar 2011-Jan 2012)

Location	# of test	# over provisional regulation values
Fukushima pref.	17,928	626
Other locations	81,260	332
Total	99,188	958

(from MHLW quick report of 2012-Jan-30)

NIRS activities at Fukushima NPP accident



Measurement of internal contamination

From the aspect of the Fukushima accident

Research Center for
Radiation Emergency Medicine
National Institute of Radiological Sciences

Toshikazu Suzuki

JAPAN

All the external sources were lost due to the earthquake of magnitude 9 that had been occurred at 14:46 March 11, 2011.

Then the emergency diesel generators were started soon in the Fukushima Daiichi NPP.

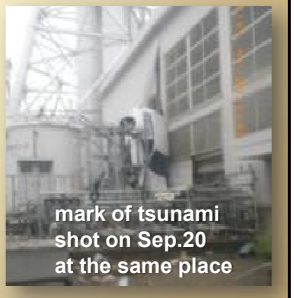
30 minutes later, the emergency diesel generators were flooded with the tsunami that exceeded 14m in height and this caused "All blackout".

All nuclear reactors were shut down automatically by the earthquake and the nuclear reaction was stopped completely.

But it was necessary to remove the residual heat that was generated with fission product in the reactor core, which could reach approx. 6.2% of thermal output of a nuclear reactor.

The residual heat removal system stopped by all blackout and this was connected with the meltdown .

raid of tsunami
at 15:10 Mar.11



mark of tsunami
shot on Sep.20
at the same place

The noble gas such as Kr- 85 and Xe-133 passed over the sky as a radioactive plume which could cause the external exposure after the hydrogen explosion or wet-well vent.

The internal exposure is not caused by them because the deposition to the organ doesn't occur even if entering the inside of the body.

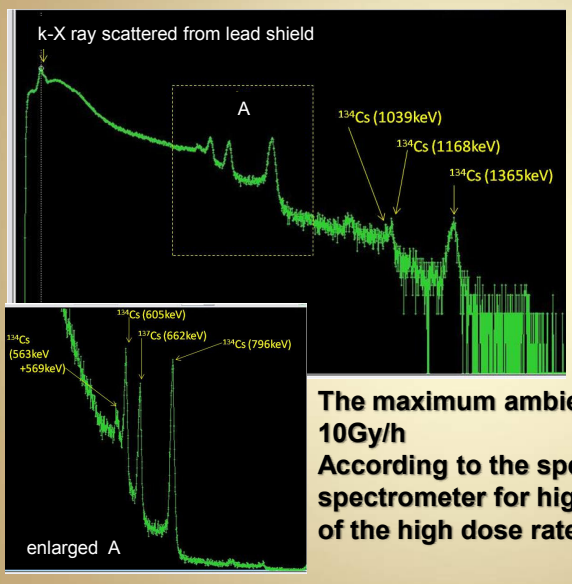
There is a possibility of causing the internal exposure when the volatile radioactive material such as Cesium or Iodine or Tellurium and particles including radioactive material is inhaled, and also the food or water polluted with the radioactive material is ingested.

hydrogen explosion of the unit 3

In case of internal exposure, the committed effective dose which is the total dose accumulated over 50 years for adult and up to 70 years old for the children is used.

For a radionuclide with an effective half-life of three months or less, the committed effective dose is approximately equal to the annual dose.

Radionuclides that caused high gamma background

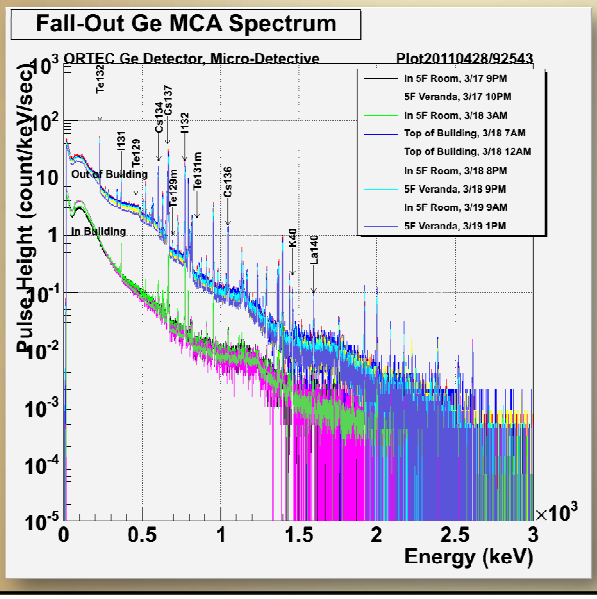


Concrete debris scattered with hydrogen explosion were the dominant gamma source for external exposure.

The maximum ambient dose rate reached 10Gy/h

According to the spectrum measurement by CZT spectrometer for high dose rate, the true colors of the high dose rate was Cs-134/137

Released radionuclide in Fukushima

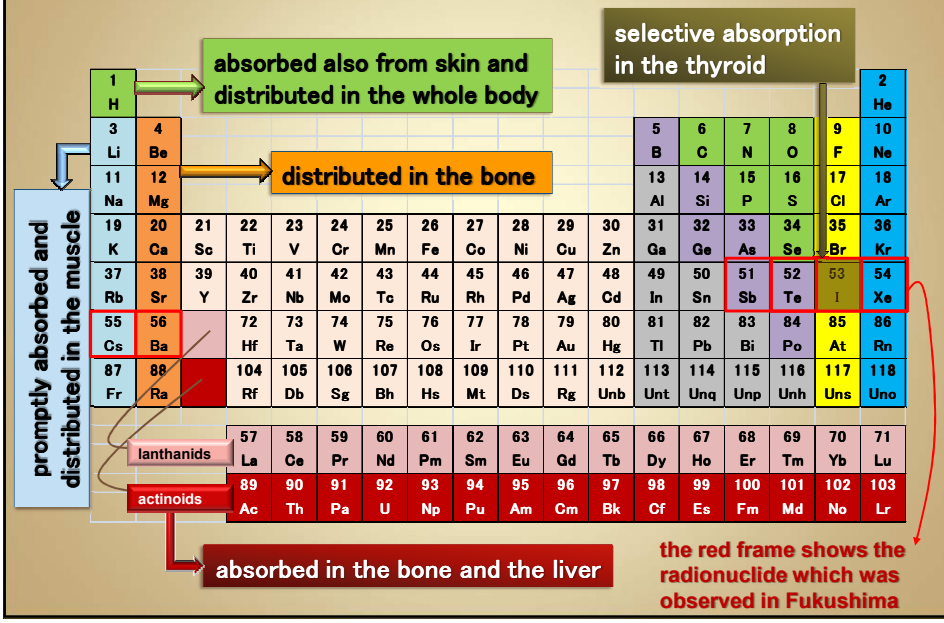


nuclide	total activity
Xe-133	1.10E+19
I-131	1.60E+17
I-135	2.30E+15
Cs-134	1.80E+16
Cs-137	1.50E+16
Te-132	8.00E+16
Te-131m	5.00E+15
Te-129m	3.30E+15
Te-127m	1.10E+15
Sb-127	6.40E+15
Sr-89	2.00E+15
Ba-140	3.20E+15

released radionuclide over 1PBq from Fukushima Daiichi NPP

National Institute of Radiological Sciences

Relation between periodic table and biokinetics



Individual monitoring

There is no difference between internal exposure and external exposure in the radiation effect as long as the same effective dose.
Effective dose E_t is evaluated by the following equation.

$$E_t = H_p(10) + \sum_j e(g)_{j,ing} I_{j,ing} + \sum_j e(g)_{j,inh} I_{j,inh}$$

external exposure

internal exposure

personal dosimeter

where, $H_P(10)$ is the personal dose equivalent,
$e(g)_{j,ing}$ is the dose coefficient for ingestion,
$I_{j,ing}$ is the intake from ingestion,
$e(g)_{j,inh}$ is the dose coefficient for inhalation,
$I_{j,inh}$ is the intake from inhalation

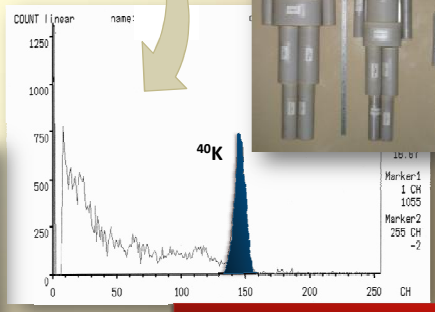
Individual monitoring for intakes is done by whole body counting or organ counting in direct methods, which can apply to gamma emitting radionuclide.
Indirect methods are applied to alpha or only beta emitting radionuclide by analysis of sample of excreta.

Whole body counting

Direct methods

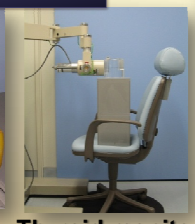
Organ counting

measure the area counts of the interest peak to compare the reference counts which was obtained by a phantom with already-known radioactivity such as BOMAB phantom



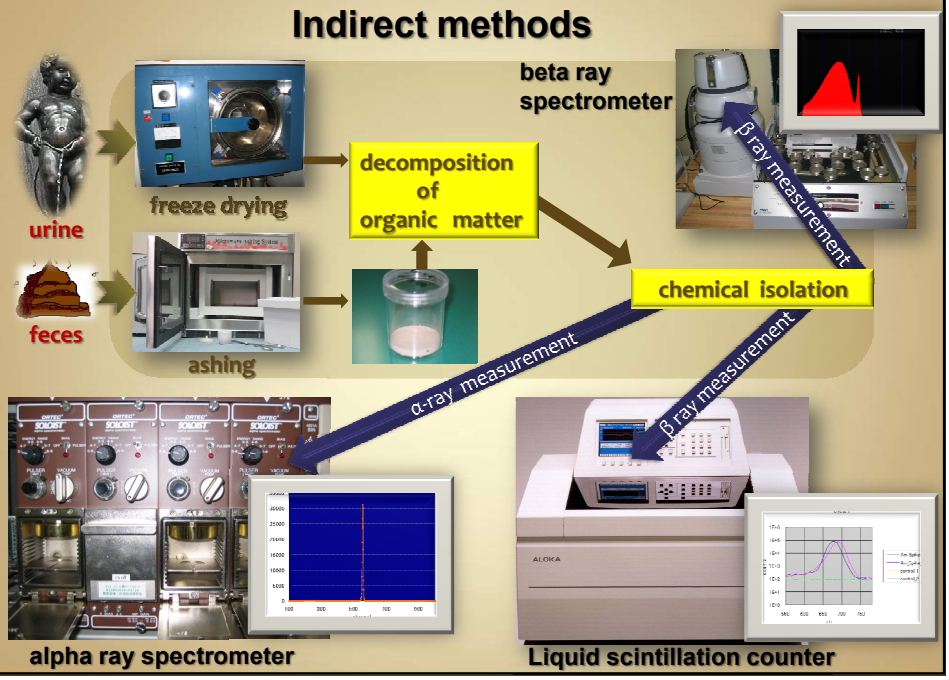
Typical spectrum obtained from normal man

Lung monitor



Thyroid monitor

Indirect methods



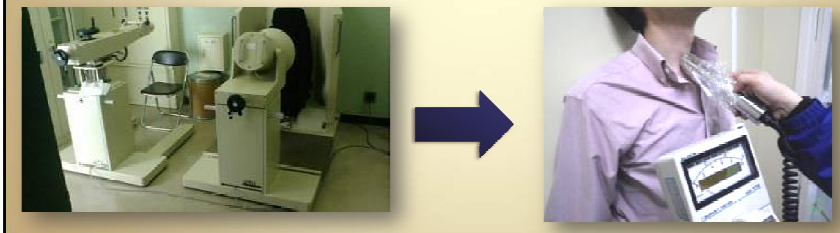
Thyroid monitoring for infants

It is an infant to receive the influence of the radioactive iodine. Over 6000 cases of thyroid cancer in infants have been reported after Chernobyl accident.

In early stage of Fukushima accident, the necessity of thyroid measurement intended for the infants was clear.

Unfortunately, the two thyroid monitors installed in radiation emergency facility which was located only 5km from Fukushima Daiichi NPP were unusable.

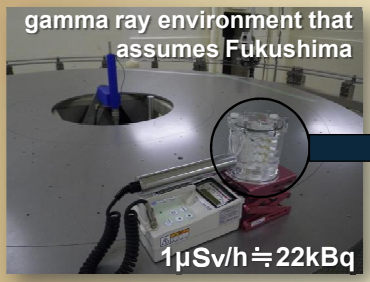
Then, the thyroid measurement using the survey meter was executed.

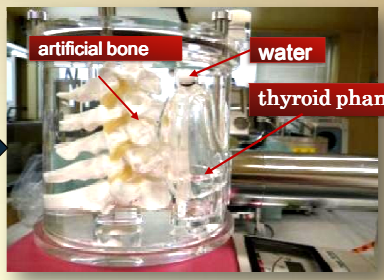


thyroid monitors left in high contaminated area

applied NaI(Tl) scintillation survey meter as substitution

Calibration and infant dose





The Ba-133 solution with the same mass of the infant thyroid gland was put in the neck phantom.
Then the conversion factor between gamma dose rate indicated by the survey meter and Ba-133 activity was decided

date	place	number of infant measured
March 26-27	Iwaki public health center	134
March 28-30	Kawamata-cho public hall	647
March 29-30	Iidate-mura public hall	299
	total	1080

No infant who exceeded 100mSv as thyroid equivalent dose

Whole body monitoring for workers

Tokyo Electric Power Company is measuring worker's internal exposure every month by operating 12 whole body counters.
1 in-vehicle type and 11 stationary

Effective dose (mSv)	internal exposure of emergency workers	total exposure of emergency workers
over 250	5	6
200–250	1	3
150–200	1	20
100–150	5	133
50–100	78	588
20–50	261	2193
10–20	686	2633
under 10	15706	11340

In-vehicle WBC

Stationary WBC

Total occupational exposure

Workers over 250mSv

6 TEPCO personnel (3 for shift operators, 3 for maintenance staff)

Maximum exposure

1 TEPCO :678.02mSv, 1 Contractor :238.42mSv

Female workers over 5mSv per 3months

2 TEPCO personnel (maximum exposure 17.55mSv)

The results of medical examination shows no impacts on their health

Analysis of high radiation exposure

- Internal exposure is dominant to workers over 250mSv
- The rapid progress of the event made it difficult for the workers to prepare for wearing proper masks.
- Charcoal filter was lacked for the loss of power and communication means
- It was late to have them given the potassium iodine tablet
- They had no choice but to eat and drink in main control room. (Emergency ventilation system in Main Control Room was installed, but it did not work due to loss of all AC power.)
- There may be gaps between masks and faces due to temples of the glasses.
- They could not respond quickly to wear masks when unexpected hydrogen explosion was occurred.

Because the majority of inventories had remained in the pressure vessel, the exposure was able to be held off at least.

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Dept. of Planning and Management

National Institute of Radiological Sciences

Anagawa 4-9-1, Inage-ku, Chiba, 263-8555, Japan

tel : +81-43-206-3025 fax : +81-43-206-4061

e-mail : kokusai@nirs.go.jp Homepage : http://www.nirs.go.jp/ENG/index.html

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NIRS

National Institute of Radiological Sciences
Dept. of Planning and Management
Interenational Affairs Section
4-9-1 Anagawa, Inage-ku Chiba-shi, Chiba 263-8555, Japan
e-mail: kokusai@nirs.go.jp
Tel:+81-43-206-3025 Fax:+81-43-206-4061
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