NIRS-M-229

PROCEEDINGS OF

II NIRS-CNAO Joint Symposium on Hadrontherapy (NIRS Experience)

Organaized by
National Institute of Radiological Sciences, Japan
and
Fondazione Centro Nazionale Adroterapia Oncologica, Italy

fondazione CNAO

NIRS

"II Symposium NIRS –CNAO"

Saturday 20 March

			E. Borloni / H. Tsujii
9.00	9.30	Introduction and Welcome	R. Orecchia and Authorities
		Opening the CNAO	*E. Barbieri / J. Debus*
9.30	10.10	Status of CNAO	E. Borloni / S. Rossi
10.10	10.30	Experimental phase at CNAO: project introduction	R. Orecchia
10.30	10.50	Discussion	
		NIRS experiences	*T. Kamada / R. Pötter*
10.50	11.20	Overview	H. Tsujii
11.20	11.40	Rectal cancer	S. Yamada
11.40	12.00	Pancreatic cancer	S. Yamada
12.00	12.20	Prostate cancer	H. Tsuji
12.20	13.00	Discussion	
		13.00 14.00 Lunch Break	
14.00	14.20	Bone and soft tissue sarcoma	T. Kamada
14.20	14.50	Head and neck tumor / Skull base tumor	A. Hasegawa
		NIRS-CNAO cooperative project	*M. Krengli / A. Kitagawa*
14.50	15.10	Medical service and Italian patients treated at NIRS	J. Mizoe
15.10	15.30	Clinical aspects of the CNAO experimental phase	P. Fossati
15.30	16.00	Physical aspects of the CNAO experimental phase	M. Ciocca
16.00	16.20	Radiobiological aspects of the CNAO experimental phase	R. Cherubini
16.20	16.40	Set - up aspects of the CNAO experimental phase	G. Baroni
16.40	17.00	Discussion	
17.00	17.30	Closing remarks	H. Tsujii / R. Orecchia

Sunday 21 March

		Radiobiological basis	*U. Ricardi / G.P. Biti*
9.00	9.20	Biological background of carbon ion RT	Y. Furusawa
9.20	9.40	Recent developments in heavy ion radiobiology	M. Durante
9.40	10.00	How to report RBE and equivalent dose	B. Chu
		New developments	*K. Noda / R. Cirio*
10.00	10.20	Design and operation of HIMAC facility	A. Kitagawa
10.20	10.50	New treatment facility project at HIMAC	K. Noda
10.50	11.10	CNAO commissioning	M. Pullia / C. Biscari
11.10	11.30	ULICE / PARTNER Overview	R. Orecchia
11.30	11.50	ULICE - Gantry design	M. Pullia
11.50	12.00	Closing remarks	H. Tsujii / R. Orecchia

Lunch Break

Visit to CNAO

12.00 13.30 there will be a transfer service from the meeting location to the CNAO facility for those who requested in the submission form

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Dear colleagues

In recent years, radiation therapy has made a startling progress with development of highly advanced, leading-edge irradiation techniques including SRT, IMRT and hadrontherapy. In the case of hadrontherapy, there are more than 30 facilities in operation and still more are in a stage of planning or under construction in the world. This is based on the fact that hadrontherapy allows a unique precision in delivering sufficient doses to the target while sparing the surrounding normal tissues. With carbon ions, there is also an additional benefit because of their radiobiological features, densely ionising, permitting to overcome the problems related to tumour radio-resistance.

At the National Institute of Radiological Sciences (NIRS) of Chiba, Japan, carbon ion radiotherapy was initiated in 1994 using the HIMAC, the world's first medically-dedicated heavy ion therapy centre. Since then, we have treated more than 5,100 patients with a variety of tumors, by which we have confirmed the therapeutic efficacy and safety of this approach in specific tumor sites.

We congratulate the hadrontherapy project of CNAO (Centro Nazionale di Adroterapia Oncologia), which successfully completed the construction of the new hadrontherapy facility in 2009. Clinical activities will soon start this year. The NIRS and CNAO, aiming at further strengthening the cooperation between the two institutes in the field of charged particle therapy, have exchanged the MOU, by which this Joint Symposium is organized. There will be full comprehensive presentation of the NIRS on clinical results and research activities, as well as presentation on an update status of the CNAO project. You can see that speakers from other institute will also participate in this meeting to exchange information and involve in discussion on charged particle therapy.

I believe that a large number of radiation oncologists, medical physicists, radiation biologists and cancer specialists could benefit from this Symposium in terms of learning, exchange of ideas and debate on indications of charged particle therapy. I do hope that you would take advantage of attending this meeting to obtain enough information and knowledge for promoting your project.

Finally, I would like to express my best wishes for the successful meeting.

Thank you

Hirohiko Tsujii
Executive Director
National Institute of Radiological Sciences

Overview of Carbon Ion Radiotherapy at NIRS

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Abstract

In June 1994, the world-first clinical center offering carbon ion radiotherapy (C-ion RT) was set to open in at NIRS, Japan. Among several types of ion species, carbon ions were chosen for cancer therapy because they were judged to have the most optimal properties in terms of superior physical dose distribution and biological characteristics. As of February 2010, a total of 5,189 patients have been registered for C-ion RT. Clinical results have shown that C-ion RT has the potential ability to provide a sufficient dose to the tumor, together with acceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to carbon ions include locally advanced tumors as well as those with histologically non-squamous cell types of tumors such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. By taking advantage of the unique properties of carbon ions, treatment with a large dose per fraction within a short treatment period has been successfully carried out for a variety of tumors. This means that the facility can be operated more efficiently in C-ion RT, offering treatment for a larger number of patients than is possible with other modalities over the same period of time.

Introduction

The structural survey of JASTRO has demonstrated that the number of cancer patients undergoing radiotherapy (RT) has increased to a total of 150,000, an equivalent to roughly 28% of all cancer patients in Japan, with forecasts that this number will continue to rise in the future (1). In recent years, the scope of diseases that can be treated with RT has significantly widened in the wake of the diffusion of high precision RT such as stereotactic RT (SRT), intensity-modulated RT (IMRT) and particle beam RT. These approaches permit administration of sufficient doses to the tumor with sparing surrounding normal tissues. In this regard, charged particles like protons and carbon ions have come to be clinically effective since R. Wilson first proposed their clinical application in 1946 (2). In the early 1950s, the clinical use of proton beams was initiated at the Lawrence Berkeley National Laboratory (LBNL), paving the way for heavy ion RT starting at the same facility in the 1970s (3, 4). At present, particle beam RT is provided at over 30 facilities worldwide, and still many more are under construction or in the planning stage.

In Japan, the decision was made in 1984 to build the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS) as an integral part of the nation's "Overall Ten-year Anti-Cancer Strategy". The accelerator complex took almost a decade to build, being completed by the end of 1993 (Fig. 1). A year later, clinical study with carbon ions for cancer therapy was initiated. Similar to the proton accelerator built at the Loma Linda University in 1990 as the first proton beam accelerator put primarily into therapeutic service, HIMAC can claim to be the world's first facility dedicated to cancer therapy using carbon ion beams. HIMAC has also been operated as a multipurpose facility available for joint use for both cancer treatment and biological, physics research.

This article reviews the clinical aspects of C-ion RT over the last decade at NIRS.

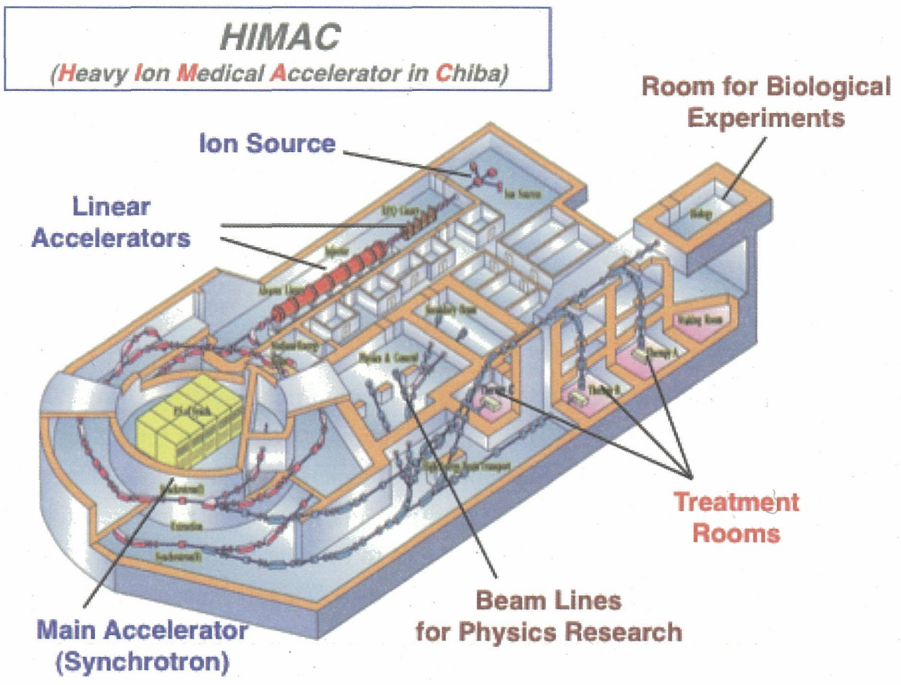

Fig. 1 The HIMAC facility at NIRS.

Characteristics of Carbon Ion Beams

Unlike X-rays, which deposit most of their energy near the skin surface, carbon ion beams are more effective in deeper tissues. The particles release the bulk of their energy as they slow down in the last few millimeters of their track, a point called the Bragg peak. The beams also scatter very little, allowing the maximum radiation dose to be precisely targeted to the tumor, thus minimizing damage to the surrounding healthy tissues.

Carbon ions also cause a different type of cellular damage from protons and photons, delivering a larger mean energy per unit length (Linear Energy Transfer: LET) of their trajectory in the body (5-7). Carbon ions directly cleave double-stranded DNA at multiple sites even at the low oxygen content, so they can tackle hypoxic parts of tumors that are resistant to RT. As a result, carbon ion beams are described as a high-LET radiation similarly to neutron beams. However, in contrast to neutron beams, whose LET remains uniform at any depth in the body, the LET of carbon ion beams increases steadily from the point of incidence in the body with increasing depth to reach a maximum in the peak region (Fig.2). This property is extremely advantageous from a therapeutic viewpoint in terms of increased biological effect on the tumor. The reason is that carbon ion beams form a large peak in the body, as the physical dose and consequently their biological effectiveness increase as they advance to the more deep-lying parts of the body. This has opened up the promising potential of their highly effective use in the treatment of intractable cancers that are resistant to photon beams.

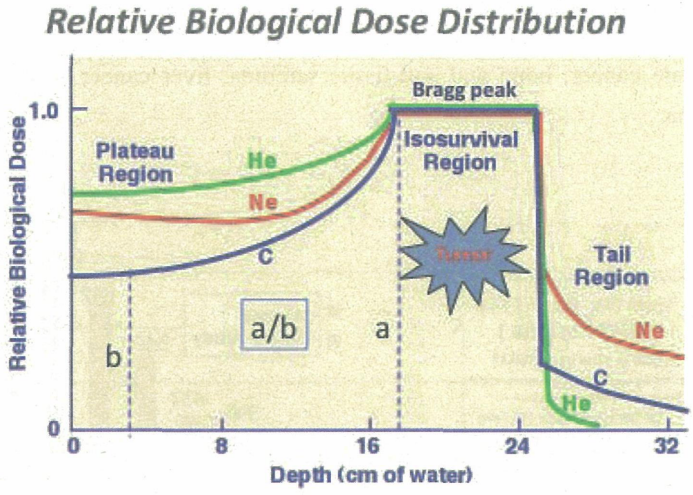

Fig. 2
Charged particles have well-localized energy deposition at the end of the beam path, called the Bragg peak, resulting in excellent dose distribution. The ratio of peak to plateau (a/b) of RBE for carbon ion beams is greater than for other ion beams, which is one of the reasons why carbon ion beams have more excellent dose distribution than other ion beams.

Carbon Ion Radiotherapy at NIRS

1. Organization for performance of C-ion RT

Consistent efforts have been made from the start to provide C-ion RT on an ethically and scientifically sound basis under the investigative control of Committees headed by the Carbon Ion Radiotherapy Network Committee as the supreme organ. All clinical protocols have been prepared by the Disease-specific Committees, checked by the Ethical Committee, and finally approved by the Network Committee. The Review Committee is appointed to deliberate on the validity of whether individual clinical trials should be continued, and the results of all clinical trials are submitted to the Network Committee whose sessions are invariably held in public.

In November 2003, the Ministry of Health, Labour and Welfare in Japan approved C-ion RT as "Highly Advanced Medical Technology (HAMT)" under the title of "C-ion RT for Solid Cancer". HAMT is designed to respond to the development of new medical technologies and to meet the diversifying needs for advanced treatment. It permits Specific Medical Institutions under the National Health Insurance System to offer advanced medical treatment, thereby enabling them to practice both general and advanced medical treatment within the National Health Insurance System. Under this scheme, care providers are able to charge their patients a special fee for advanced treatment in addition to the ordinary personal share of the medical fee payable by the patient himself under the National Health Insurance System. The treatment fees for HAMT were calculated on the basis of the incidental cost factors, including the construction costs of HIMAC, personnel costs, costs for the materials used for treatment, accelerator operating costs (water, electricity, lighting, etc.) and the expenditures for maintenance and management of running the facility.

2. Patients and treatment techniques

1) Patient characteristics

C-ion RT at NIRS was initiated in June 1994. Up to the present, more than 50 protocols have been established, and phase I/II and II trials have been conducted in an attempt to determine the optimal dose-fractionations and irradiation techniques for each specific tumor (8-11). The number of patients has increased year-by-year, and the facility has meanwhile reached a capacity permitting more than 750 cases to be

treated each year (Fig. 3). The registration of patients has reached a total of 5189 as of February 2010 (Fig. 4). The categories of disease which can be treated in the HAMT scheme include skull base tumor, head and neck cancer, lung cancer, prostate cancer, bone and soft-tissue sarcoma, liver cancer, pelvic recurrences of rectal cancer, and uveal melanoma.

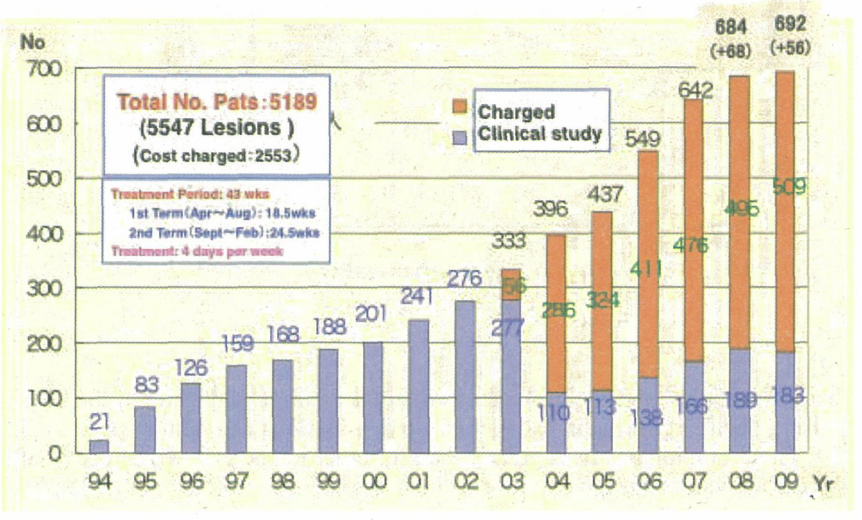

Fig. 3
Annual number of patients treated with carbon ion radiotherapy at NIRS (21/06/1994 – 8/02/2010). Red bars indicate the patients treated under HAMT, and the blue bars the patients treated in clinical trials.

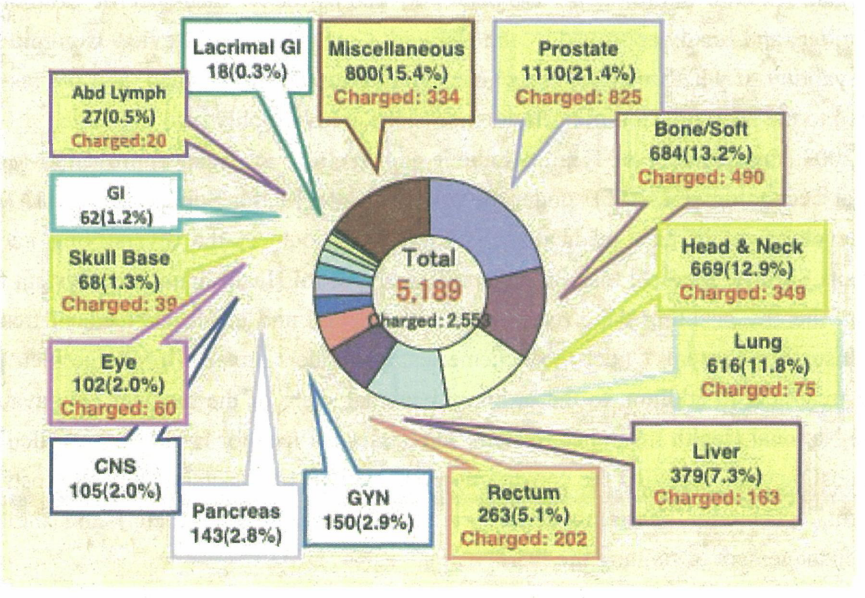

Fig. 4 Distribution of tumor sites treated with carbon ion RT (21/06/1994 – 28/02/2010).

2) Irradiation techniques

When the patient is referred to our institute, a preliminary screening process takes place to determine whether or not the particular patient is eligible for C-ion RT under any of the disease-specific protocols. This requires close coordination and consultation with the referring physician. When the decision has been reached that the criteria for patient eligibility are met, the patient is provided with detailed explanations about the possible side effects of treatment and the prospect of the therapeutic outcome in order to obtain the patient's informed consent. The signed consent form is then submitted to the Ethics Committee together with all other necessary documentation. The Committee thereupon deliberates on patient eligibility, and the preparatory steps for treatment will not be initiated until the Committee's approval has been granted.

The first preparatory step to ensure the proper administration of C-ion RT is the fabrication of an immobilizing device for each individual patient. A CT scan for treatment planning is then taken with the patient wearing the immobilizing device (Fig. 5). If the patient requires respiration-synchronized irradiation, the respiration synchronizing system must also be applied at the time of this CT scan (12). The CT image data obtained in this manner are then transferred to the treatment planning system known as HIPLAN (13). At this stage, the irradiation parameters in terms of the number of irradiation portals and irradiation direction are determined in conjunction with the localization of the target volume. Based on this, dose distribution is calculated using HIPLAN. Once the patient-specific irradiation parameters have been determined, the next step is to design the bolus and collimator for the selective irradiation of the tumor strictly in accordance with these parameters.

a b

Fig. 5
(a) CT scans for treatment planning are performed with the patient wearing immobilization devices.
(b) Control console.

Based on these preparations, the patient-specific irradiation parameters and dose distribution have now been determined and the calculation results are presented to the Review Board for Treatment Planning, which examines their appropriateness. In many instances, the outcome of these deliberations will be a review request, and on many occasions, a complete redoing of the treatment planning may also be required. Clearly, if such review or redo requests are made very frequently, the entire work schedule may be affected, and it is therefore essential to examine the treatment parameters with the most meticulous care beforehand. After the irradiation parameters applicable to a particular patient have been determined and the bolus and collimator have been fabricated, the final preparations for therapy can now take place by measuring the radiation dose under the same conditions as for the actual RT session and carrying out a mockup rehearsal, followed by delivery of irradiation (Fig. 6).

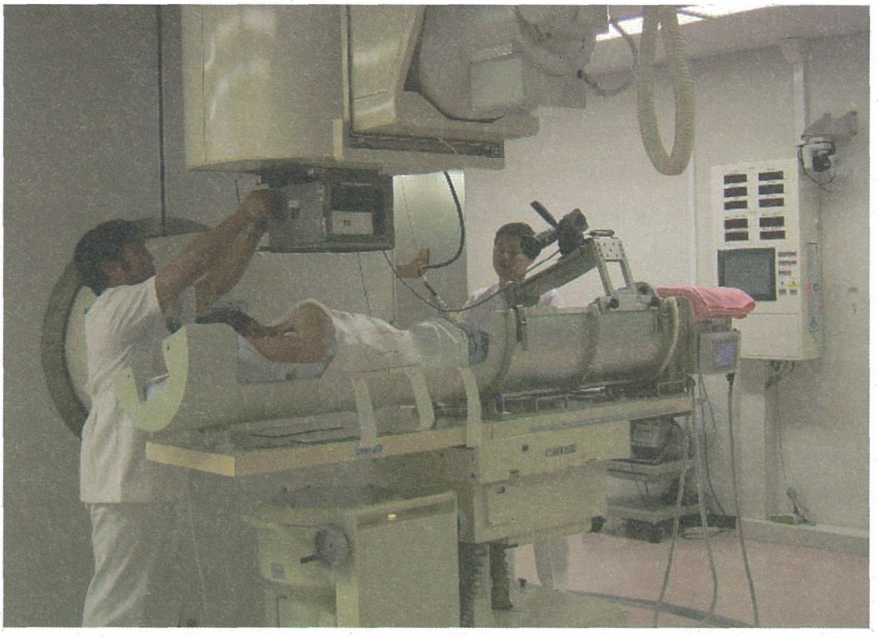

Fig. 6 Treatment room

3) Dose prescription

In C-ion RT it is necessary to spread out the narrow peak to fit the target volume. Metal ridge filters are used for producing the spread-out Bragg peak (SOBP), and the shape of the SOBP has to be designed so that the target volume will be irradiated uniformly within the peak. The practice is to use HSG cells, which are parotid cancer cells, as substitutes of the tumor cells, to design the dose distribution in such a manner that they will be killed uniformly in the SOBP (14-15). The dose is indicated in GyE, a unit calculated by multiplying the physical carbon ion dose with the RBE value so as to permit its comparison with photon beams: GyE = Physical dose x RBE. It should be pointed out here that the RBE of the carbon ion beams used for RT is 3.0 at the distal part of the SOBP. This value is identical to the RBE determined for the neutron beam RT previously provided at NIRS (15).

As biological dose distribution is flat within SOBP, once the RBE values have been determined at a given position, they are easily calculated at any position by dividing the biological dose by the physical dose. RBE of carbon ions was estimated to be 2.0∽3.0 along SOBP for acute skin reactions. As seen in Fig. 7, a clinical dose of 2.7 Gy (E) would be given at any position within SOBP; for example, a physical dose of 0.9 Gy carbon ions at the 8-mm upstream position would give an RBE value of 2.7/0.9 = 3.0, whereas 1.13 Gy at the middle of SOBP should bring an RBE value of 2.7/1.13 = 2.4.

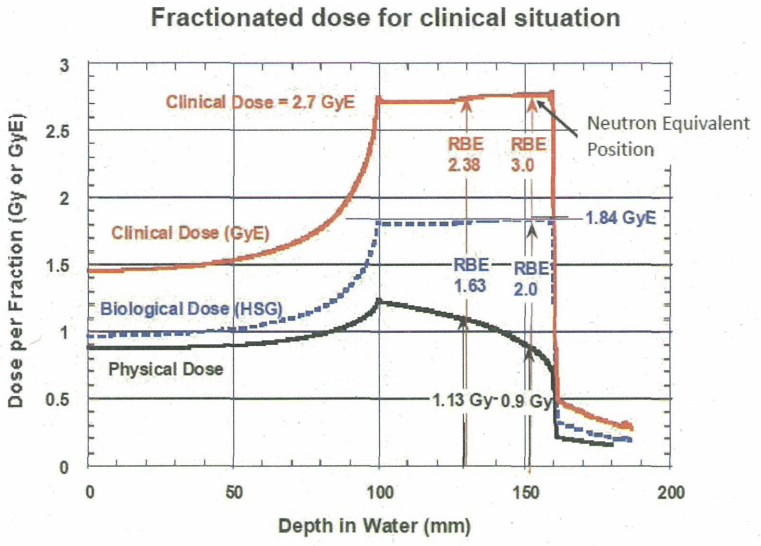

Fig. 7
Experimental and clinical RBE of 290 MeV/u carbon-ion beams with a 6-cm SOBP.

4) Dose fractionation

C-ion RT at NIRS is available four days a week (Tuesday through Friday). In recent years, Monday has become available on a once-a-month basis for tumors treatable in a single fraction, and this also facilitated an increase in the annual patient number load. HIMAC is in principle closed for therapy on weekends as well as on Mondays, when the accelerator is subjected to maintenance or is used for physical and biological experiments.

The radiotherapeutic approach of our treatment has been to fix both the total number of fractions and the overall treatment time for each tumor. In dose escalation studies, we escalated the dose in incremental steps of 5 or 10% at a time. After the recommended dose thus became established in phase I/II trials, the transition to phase II trials was made. Supposing that a fractionation regimen of 16 fractions spread over four weeks had been selected and that a total dose of 57.6 GyE had been increased by 5% to 60.5 GyE, this would have meant that the dose per fraction would have been stepped up from 3.6 GyE to 3.8 GyE, in light of the fact that the irradiation time and fraction number had been fixed. Once the recommended dose resulting from the dose escalation trial has been decided, phase II trials or Advanced Therapy can then be initiated with this recommended dose.

In view of the unique physical and biological properties of carbon ions, it is theoretically possible to perform hypofractionated RT consisting of only a few irradiation sessions. In contrast, experiments with neutron beams that have the same high-LET components as carbon beams have demonstrated that increasing their fraction dose tended to lower the RBE for both the tumor and normal tissues. In these experiments, however, RBE for normal tissues does not decrease as rapidly as that for the tumor (16). This experimental result substantiates the previous observation that the therapeutic ratio increases rather than decreases even though the fraction dose is increased. Similar results have also been obtained in experiments conducted with carbon ion beams at NIRS (17,18). They have provided biological evidence for the validity of the short-course hypofractionated regimen with C-ion RT.

5) Results of treatment by tumor type

As stated above, carbon ion beams have a therapeutically favorable biological dose distribution. Utilizing these properties makes it possible to complete the therapy in a short time. As is seen in Table 1, progress in dose escalation has already been made on a scale that permits the RT course for stage I lung cancer and liver cancer to be completed in 1 or 2 irradiation sessions, respectively. Even for prostate cancer and bone and soft tissue

tumors that require a relatively prolonged irradiation time, it is possible to accomplish the treatment course with carbon ion beams in 16 fractions over 4 weeks, only half the fraction number and time required for x-ray and proton beam therapy. At present, the average number of fractions and the treatment time per patient is 12.5 fractions and 3 weeks, respectively. As shown in Fig. 3, the number of registered patients has been steadily increasing year after year. Apart from the fact that the irradiation methods have been firmly established and therapy can be administered without difficulty, this may be ascribed to the significant shortening in the number of fractions and overall treatment time per patient.

Site		GyE / Fr./ Wk	GyE / fr	BED (α/β=10)	BED (α/β=2.5)
Head & Neck	Adenoca, ACC, MMM Sarcoma	57.6 / 16 / 4 70.4 / 16 / 4	3.6 4.4	78.3 101.4	140.5 194.3
Skull base	Chordoma & Chondrosarcoma	57.6 / 16 / 4	3.6	78.3	140.5
Lung	Peripheral	60.0 / 4 / 1 46.0 / 1 / 1dy	15.0 -	150.0 -	420.0 -
Lung	: Mediastinum Hilar : Superficial : Bulky	48.0 / 12 / 3 54.0 / 9 / 3 68.4 / 12 / 3	4.0 6.0 5.7	67.2 86.4 107.4	124.8 183.6 224.4
Liver	Hepatocellular ca Metastasis of Rectal ca	42.8 / 2 / 2dys > 46.0 / 1 / 1dy	21.4 -	134.4 -	409.2 -
Bone & Soft tissue	Sarcoma	70.4/ 16 / 4	4.4	101.4	193.4
Prostate	Low/Medium/High risk	57.6 /16/ 4	3.6	78.3	140.5
Pancreas	Pre-operative RT C-ion+CDDP 1000mg/m²	> 35.2 / 8 / 2 > 45.6 / 12 / 3	4.4 3.8	50.7 62.9	97.2 114.9
Rectum	Post-ope pelvic rec.	73.6 / 16 / 4	4.6	107.5	209.0
Standard photon RT		60 / 30 / 8	2.0	72	108

Table 1. Dose-fractionations determined in dose escalation studies at NIRS

In terms of toxic reactions (side effects), significant progress has been made, as the toxicities initially associated with dose escalation such as ulceration and perforation of the gastrointestinal tract requiring surgery are no longer encountered in the wake of improvements in irradiation techniques.

Our experience to-date can be summed up by characterizing C-ion RT as follows: 1) By location, it is effective in tumors of the head and neck (including the eye), the base of the skull, lung, liver, prostate, bone and soft tissue, and pelvic recurrence of rectal cancer. 2) By pathological type, it is effective against pathologically non-squamous cell types of tumors for which photon beams are little effective, including adenocarcinoma, adenoid cystic carcinoma, hepatocellular carcinoma, and sarcomas (malignant melanoma, bone and soft-tissue sarcoma, etc.). For certain cancers such as malignant melanoma of the head and neck and pancreatic cancer, it was important to develop methods for preventing distant metastasis so as to improve the survival rate still further. In this context, C-ion RT combined with chemotherapy has been carried our in these tumors. So far, the results have been very promising.

Summary

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

So far, with the support of the many members concerned both inside and outside the Institute, a substantial amount of evidence has been accumulated in terms of the safety and efficacy of C-ion RT for various types of

malignant tumors including non-squamous cell types of tumors. One of the most important objectives in these endeavors has been to determine, in particular, the validity and limits of hypofractionated, accelerated RT. Furthermore, at the end of 2003, the Institute was successful in obtaining approval for the Highly Advanced Medical Technology (HAMT) from the government. This was an important landmark for widening the scope of diseases corresponding to C-ion RT. In this manner, C-ion RT has meanwhile won for itself a solid place in general medical practice, with the next target being that of obtaining approval for this therapy to be included in general practice under the National Health Insurance scheme.

References

[1] Shibuya H, Tsujii H: The structural characteristics of radiation oncology in Japan in 2003, 27 April 2005. Int J Radiat Oncol Biol Phys. 62: 1472-1476, 2005.

[2] Wilson RR: Radiological use of fast protons. Radiology. 47:487-491, 1946.

[3] Linstadt DE, Castro JR, Phillips TL: Neon ion radiotherapy: results of the phase I/II clinical trial. Int J Radiat Oncol Biol Phys. 20:761-769,1991.

[4] Castro JR: Future research strategy for heavy ion radiotherapy. Progress in Radio-Oncology. (ed. Kogelnik HD), Monduzzi Editore, Italy, pp643-648, 1995.

[5] Raju MR: Heavy particle radiotherapy. Academic Press, New York, 1980.

[6] Chen GTY, Castro JR, Quivey JM: Heavy charged particle radiotherapy. Ann Rev Biophys Bioeng. 10: 499-529, 1981.

[7] Kraft G: Tumor therapy with heavy charged particles. Prog Part Nucl Phys. 45: S473-S544, 2000.

[8] Tsujii H, Morita S, Miyamoto T, et al: Preliminary results of phase I/II carbon-ion therapy at the NIRS. J Brachytherapy Int. 13: 1-8, 1997.

[9] Tsujii H, Mizoe J, Kamada T, et al: Overview of clinical experiences on carbon ion radiotherapy at NIRS. Radiother Oncol. 73(Suppl 2): S41-S49, 2004.

[10] Tsujii H, Mizoe J, Kamada T, et al: Clinical results of carbon ion radiotherapy at NIRS. J Radiat Res. 48 (Suppl A): A1–13, 2007

[11] Tsujii H, Kamada T, Baba M, et al: Clinical advantages of carbon-ion radiotherapy. New J Phys. 10: 1367-2630, 2008.

[12] Minohara S, Kanai T, Endo M, et al: Respiratory gated irradiation system for heavy-ion radiotherapy. Int J Radiat Oncol Biol Phys. 47: 1097-1103, 2000.

[13] Endo M, Koyama-Ito H, Minohara S, et al: HIPLAN - a heavy ion treatment planning system at HIMAC. J Jpn Soc Ther Radiol Oncol. 8: 231-238, 1996.

[14] Kanai T, Furusawa Y, Fukutsu K, et al: Irradiation of mixed beam and design of spread-out bragg peak for heavy-ion radiotherapy. Rad Res. 147: 78-85, 1997.

[15] Kanai T, Endo M, Minohara S, et al: Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys. 44: 201-210, 1999.

[16] Denekamp J, Waites T, Fowler JF: Predicting realistic RBE values for clinically relevant radiotherapy schedules. Int J Radiat Biol. 71: 681-694, 1997.

[17] Koike S, Ando K, Uzawa A, et al: Significance of fractionated irradiation for the biological therapeutic gain of carbon ions. Radiat Prot Dos. 99: 405-408, 2002.

[18] Ando K, Koike S, Uzawa A, et al: Biological gain of carbon-ion radiotherapy for the early response of tumor growth delay and against early response of skin reaction in mice. J Radiat Res. 46:51-57, 2005.

Carbon Ion Therapy for Patients with Locally Recurrent Rectal Cancer

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Abstract

Purpose: To evaluate the tolerance for and effectiveness of carbon ion radiotherapy in patients with locally recurrent rectal cancer.

Patients and Methods: We conducted a phase I/II dose escalation study of carbon ion radiotherapy. One hundred patients with 105 sites of locally recurrent cancer receiving carbon ion radiotherapy were analyzed. Forty-eight relapses originated in the presacral region, 28 in the pelvic sidewalls, 16 in the perineal region and 8 in the colorectal anastomosis. The total dose ranged from 67.2 to 73.6 gray equivalent (GyE) and was administered in 16 fixed fractions over 4 weeks (4.2 to 4.6 GyE/fraction).

Results: None of 75 patients treated with the highest total dose of 73.6 GyE experienced National Cancer Institute - Common Toxicity Criteria grade 3 to 5 acute reactions. The local control rate in patients treated with 73.6 GyE in the present study was 97% at one year and 92% at 3 years. Dose escalation was then halted at this level. The median survival time in patients treated with 73.6 GyE was 54 months (range, 7 to 65 months), and the 1- and 3-year overall survival rates were 71% at 3 years and 39% at 5 years, respectively.

Conclusion: Carbon ion radiotherapy seems 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.

Introduction

The major recurrence patterns after surgery for rectal cancer include liver metastasis and local recurrence, with the rate of local recurrence (LR) for rectal cancer ranging from 10 to 40% [1-3]. Although the use of pre- or postoperative radiation therapy has reduced the incidence of LR, 10-15% of patients still develop recurrence. Patients with locally recurrent rectal cancer have low rates of subsequent local control and overall survival. Surgical resection remains the only potentially curative treatment. Curative surgery of LR is technically difficult and the rates of complications and operative mortality are relatively high. In fact, surgery of LR is seldom feasible, and most patients are referred for radiotherapy. External-beam radiation therapy is generally considered a palliative treatment. LR is resistant to conventional radiotherapy and is located close to critical organs.

The carbon ion beam possesses unique physical and biologic properties [4,5]. It has a well-defined range and insignificant scatter in tissues, and the energy release is enormous at the end of its range. This well-localized energy deposition (high-dose peak) at the end of the beam path, called the Bragg peak, is a unique physical characteristic of charged particle beams, as is the induction of more cell cycle- and oxygenation-independent, irreversible cell damage than that observed with low-LET radiation. To improve long-term local control and

survival of locally recurrent rectal cancer, we have initiated a radiation dose-escalation trial using carbon ion beams.

Patients and Methods

Patient Eligibility

Patients were included in the study if they were confirmed with locally recurrent rectal cancer without distant metastasis by computed tomography (CT), magnetic resonance imaging (MRI), and carbon-11-methionine positron emission tomography (PET) findings, had adenocarcinoma of the rectum and had a potentially curative resection of the primary tumor and regional lymph nodes performed with neither gross nor microscopic residual disease. Patients who had undergone chemotherapy within 4 weeks before carbon ion radiotherapy or those who had prior radiation therapy at the same site were excluded from the study. The tumor had to be grossly measurable, but the size could not exceed 15 cm. Eligibility criteria included a Karnofsky performance status score higher than 60 and estimated life expectancy of at least 6 months. Exclusion criteria were having another primary tumor, and infection at the tumor site and digestive tract in contact with the clinical target volume. A complete history was obtained and a physical examination was performed before registration, including CT, MRI and PET to determine the extent and size of the tumor. Chest and upper abdominal CT scans were mandatory at the time of entry into the trial. All patients signed an informed consent form approved by the local institutional review board.

Carbon Ion Radiotherapy

The Heavy Ion Medical Accelerator in Chiba is the world's first heavy ion accelerator complex dedicated to medical use in a hospital environment. The features of the accelerator and carbon ion beam have previously been described [6,7]. In brief, carbon ion radiotherapy was given once daily, 4 days a week (Tuesday to Friday), for fixed 16 fractions in 4 weeks. Patients were treated with two to five irregularly shaped ports (median, three ports). The clinical target volume (CTV) was determined by setting the margin 5mm outside the gross tumor volume (GTV) and included the regional lymph nodes (LN). The LN areas that should be considered part of the target volume include the internal iliac, external iliac and presacral nodes. Dose constraints of the maximum dose for the intestine and bladder were 30 GyE in 9 fractions and 60 GyE in 16 fractions, respectively. Prophylactic nodal areas of risk are usually treated with 37.8-41.4 GyE in 9 fractions of 4.2-4.6 GyE before irradiation field are reduced in size.

Dose Escalation and Toxicity Criteria

At least three patients were treated at the same dose level, and then a 10% escalation of the total dose was carried out after careful observation of normal tissue responses using to NCI-CTC (National Cancer Institute - Common Toxicity Criteria Version 2.0). Dose adjustment was planned if there was any acute RTOG grade 3 or higher toxicity. We followed the standard phase I dose escalation methods. If no dose-limiting toxicity (DLT) was observed in any of the three patients at a given dose level, the dose level was escalated for the next cohort. If DLT was observed in no more than one in three patients, then three more patients were treated at the same dose level. If no further cases of DLT were seen in the additional patients, then the dose level was escalated for the next cohort. Otherwise, dose escalation was stopped. Three patients at any dose level of each site had to be followed up for at least 3 months before a subsequent dose escalation. We used 67.2 GyE in 16 fractions, 4.2 GyE/fraction as the starting dose. For late reactions, the Late Effects of Normal Tissues/Subjective, Objective, Management, and Analytic scoring system was used in addition to the RTOG/European Organization for Research and Treatment of Cancer late scoring system. Scores for late reactions were the highest observed 3 months or later after carbon ion radiotherapy.

Toxicity

Toxicity on organs such as the skin, bladder and digestive tract was assessed according to NCI-CTC Version 2.0 (April 30, 1999) and RTOG/EOTRC (late) classification.

Tumor Response and Local Control Criteria

Tumor response was defined as the maximum tumor response observed by the RECIST scoring system during the first 6 months after the initiation of carbon ion radiotherapy. Complete response (CR) was defined as the disappearance of all measurable tumor in the treatment volume. Partial response (PR) meant a 30% or greater decrease in tumor size (longest diameter). Stable disease was that with a less than 30% decrease or a less than 20% increase in tumor size. Progressive disease was defined as a 20% or greater increase in tumor size. The absence of local failure in the treatment volume based on CT, MRI, and PET scans was described as local control. Local recurrence was defined in terms of lesions occurring in the tumor bed.

Follow-Up

All patients were seen on a regular basis during follow-up. Initial evaluation of tumors using CT, MRI, and PET scans was performed within 1 month after the completion of carbon ion radiotherapy. Thereafter, the patients were followed up by CT or MRI every 1 or 2 months for the next 6 months, and then the intervals between imaging and follow-up were extended to 3 to 6 months. PET was not performed regularly after the initial evaluation.

Statistics

Survival time and local control time were defined as the interval between the initiation of carbon ion radiotherapy and the date of death or the date of diagnosis of local failure, respectively. The survival and local control curves were generated by Kaplan-Meier method and the log-rank test was used for comparisons.14,15 Results were considered significant at $P < 0.05$.

Results

Patient Characteristics

Between April 2001 and February 2008, 103 patients (108 lesions) were enrolled into this study. One patient was excluded because of subarachnoid hemorrhage before treatment. Thus, 102 patients of 103 eligible patients were treated with carbon ion radiotherapy. Two more patients were excluded because of peritoneal dissemination or lymph node metastasis of the mediastinum. Thus, 105 lesions in 100 patients (65 men and 35 women) were treated with carbon ion radiotherapy. Patient characteristics are summarized in Table 1. Median age was 62.5 years (range 27 to 83 years). All patients presented with adenocarcinoma at initial surgery. Abdominoperineal resection had been performed in 56 patients, anterior resection in 42, and Hartmann's resection in two. Forty-eight relapses originated in the presacral region, 28 in the pelvic sidewalls, 16 in the perineal region, and 8 in the colorectal anastomosis. Carbon beams of 290, 350 and 400 MeV/nucleon energy were generated by the HIMAC synchrotron. Carbon ion therapy was given once daily, 4 days a week, for fixed 16 fractions in 4 weeks. The dose was set at 67.2 GyE (4.2 GyE per fraction) and escalated to 73.6 GyE (4.6 GyE) at 5% increments.

Toxicity

Toxicities in the 102 patients (107 lesions) receiving carbon ion therapy are listed in Table 2. They were relatively few and mild in these patients. All patients completed the scheduled treatment course. No grade 3 to 5 acute toxicity was observed. Two grade 3 late skin and one gastrointestinal reactions were observed among the 124lesions.

Characteristics	No. of Pts. (N=119,124lesions)
Age, years	
Median	62.5
Range	27-83
Female/Male	74/38
Primary tumor operation	
abdominoperineal excision	65
low anterior resection	52
Hartmann's resection	2
Tumor sites (n=59)	
presacral	52 (+1)
lymph nodes	42 (+2)
perineal	17 (+1)
anastomotic	8 (+1)

Table 1. Patient Characteristic

	Acute (NCI-CTC)						Late (RTOG/EORTC)					
	No. of lesions	Gr0	Gr1	Gr2	Gr3	Gr4	No. of lesions	Gr0	Gr1	Gr2	Gr3	Gr4
Skin	127	24	96	7	0	0	127	55	69	1	2	0
Gastrointestinal	127	125	1	1	0	0	127	125	0	1	1	0
Urinary	127	126	1	0	0	0	127	125	0	2	0	0

Table 2. Acute and Late Toxicities by NCI-CTC and RTOG/EORTC Scoring System

MTD of 73.6 GyE had been indicated for patients with bone and soft-tissue sarcomas in the pelvis by a phase I/II dose escalation study of carbon ion radiotherapy. The local control rate in patients treated with 73.6 GyE in the present study was 98% at one year and 95% at 3 years, significantly better than the hitherto reported local control rates. The patients in our series had been considered mostly to have tumors for which there were no other effective local treatments. Despite such dire conditions, patients experienced good tumor control and a relatively low incidence of complications with carbon ion radiotherapy. To confirm these findings, a phase II clinical trial using 73.6 GyE is warranted.

Despite the fact that various types of chemotherapies were applied before or after carbon ion radiotherapy, there were no obvious effects of chemotherapy on the incidence of toxicities in this series.

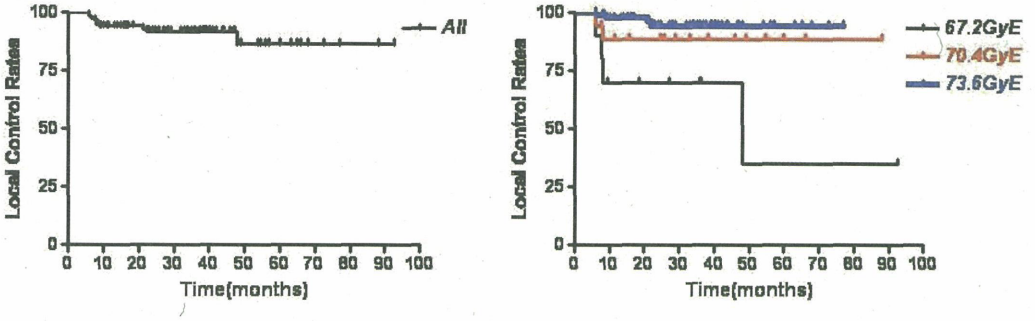
Tumor Response

Evaluation of tumor response was not considered the primary endpoint of this study. Tumor response was evaluated in 124 lesions. One patient was excluded from tumor response analysis because of difficulty in imaging evaluation. CR was observed in 16 lesions and PR in 33 (Table 3). Sixty lesions remained stable. The overall tumor response rate (CR+PR) was 40%. Remarkable anti-tumor effects were observed.

Total dose (GyE)	No. of lesions	CR	PR	SD	PD
67.2	10	4	1	5	0
70.4	20	0	8	12	0
73.6	94	12	26	56	0

Table 3. Tumor Response of 124 Lesions

The overall actuarial local control rates at five years were 35%, 89% and 95% at 67.2 GyE, 70.4 GyE and 73.6 GyE, respectively. Ten in-field recurrences were observed among the recurrent patients (Fig.1).

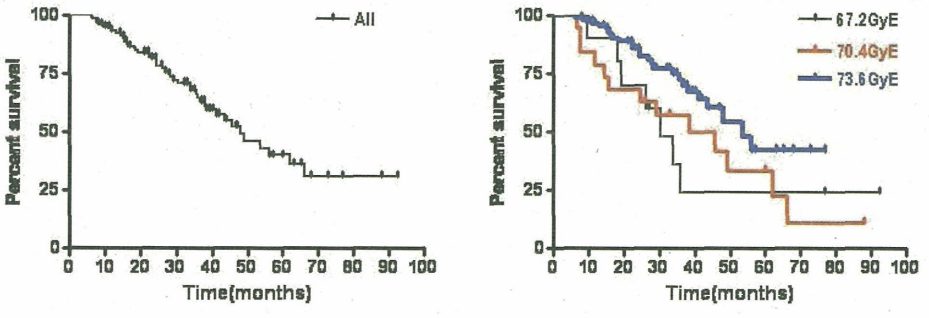


(a) (b)

Fig. 1. Local control rates a) in all 124analyzed lesions, b) by total dose

In terms of symptomatic response within 3 months after treatment, pain improved in 97% of the symptomatic cases. Pain relief was maintained at one year in 67%, 91% and 100% of the patients treated with 67.2GyE, 70.4GyE and 73.6GyE, respectively. In general, symptoms tended to improve during the course of radiation rather than worsen. While most authors agree that irradiation is frequently an effective therapy for symptomatic pelvic tumors, it has also been established that the response usually persists for only about 3-6 months. Symptomatic response rates range from 50% to 94%.

The overall survival estimates for the 119 analyzed patients are shown in Fig 2. The three-year and five-year overall survival rates were 66% and 40%, respectively. The overall survival rates at three years were 36% at 67.2 GyE, 57% at 70.4 GyE, and 73% at 73.6 GyE. There was a clear correlation between overall survival rates and total dose.



(a) (b)

Fig. 2. Overall survival rates a) in all 119 analyzed patients, b) by total dose

Our survival rate data are nearly the same as those associated with surgical resection.

The above results substantiate the superior usefulness of heavy ion radiotherapy in the treatment of recurrent rectal cancer to conventional photon radiotherapy or combinations with chemotherapy.

Discussion

In this study, carbon ion radiotherapy was well tolerated and demonstrated substantial activity against locally recurrent rectal cancer. These results were obtained in patients with advanced and/or chemoresistant gross lesions not suited for surgical resection.

We found a dose-response relationship for local control at each year. The rate of actuarial local control increased as the total dose increased from 67.2 to 73.6 GyE, reaching more than 90% in patients treated with 73.6 GyE at one year. The 3-year local control rate for patients receiving either 70.4 GyE or 73.6 GyE was similar at 89 or 95%, significantly better than that for those receiving 67.2 GyE (Fig. 3). Surgery is considered the standard treatment for rectal cancer patients but is only possible in a very small number of cases. Curative surgery for recurrent rectal cancer has resulted in higher than 50% long-term local control rate [8,9]. However, most patients must be referred to radiotherapy. There have been several attempts to improve the duration and quality of response in advanced cancers by combining radiation treatment with chemotherapy [10-13]. Previous studies reported local control rates in patients with locally recurrent rectal cancer treated by all types of radiotherapy including other particle beams of less than 50% [14,15]. The local control rate of our 73.6 GyE group could be among the best achieved without surgical resection.

Although the focus of this study was not directed at survival duration, nonetheless, it is noteworthy that improved local control resulted in better survival. We found a dose-response relationship for the survival rate. The 2-year overall survival rate increased as the total dose increased from 67.2 to 73.6 GyE. The 2- and 5-year overall actuarial survival rates were 86% and 42% respectively; in the literature, the reported 2-year survival rate for patients with locally recurrent rectal cancer treated by external-beam radiation was 45% or less (table4). External-beam radiation therapy alone or in combination with chemotherapy provides palliation and modest prolongation of life but has only a minimal curative potential in patients with locally recurrent rectal cancer. The reported 2- year and 5-year overall survival rate in patients with locally recurrent rectal cancer treated by curative surgery were 62-78% and 20-39% respectively(table5). This level of survival rate achieved with carbon ion RT can be considered as equivalent to or better than surgical resection.

Study and Reference		Number of patients	Radiation dose(Gy)	Survival rate 2y	Survival rate 5y	Local control rate
Ciatto S [10]	1982	108	35-50Gy	5%(3y)	3%	
O'Connell [11]	1982	17	50	45%	0%	24%(2y)
Wong CS [12]	1991	22	45-50	27%	16%	9%(5y)
Lybeert MLM [13]	1992	76	6-66	61%(1y)	13%(3y)	28%(3y)
Knol HP [14]	1995	50	60	27%	8%	
Murata [15]	1997	18	12-60	44%(1y)		46%
NIRS	2010	99	73.6	87%	45%	95%(5y)

Table 4. Results on the Radiation Therapy of Locally Recurrent Rectal Cancer

Study and Reference	Number of patients	Survival rate 1 y	Survival rate 2 y	Survival rate 5y
Wanebo [9] 1999	53	91%	62%	31%
Salo JC [16] 1999	71	88%	75%	31%
Saito N [17] 2003	43	91%	78%	39%
Moriya [18] 2004	48	95%	76%	36%
Melton [19] 2007	29	92%	65%	20%
NIRS 2010	99	97%	87%	45%

Table 5. Results on the Surgical Treatment of Locally Recurrent Rectal Cancer

Wendling has clearly shown that the oxygenation of differential rectal adenocarcinoma is distinctly lower than that of the normal rectal mucosa, and tissue hypoxia or even anoxia are common features of these tumors [16]. Furthermore, Hockel showed that there is significantly greater hypoxia in pelvic recurrence than in primary tumors [17]. Improvements in tumor response and control have been sought through efforts to overcome the radioresistance of the hypoxic tumor cells identifiable in rectal cancers. These aspects might give high-LET particles a particular advantage, no matter whether this is due to a lower oxygen enhancement ratio (OER) or other intrinsic factors. Therefore, high-LET particle radiotherapy such as carbon ion or neutron seems to be effective against recurrent tumor, which is hypoxic. Twenty patients with recurrent rectal cancer were treated using the d,T generator in Munster by combined neutron-radiotherapy [18]. The radiation schedule most often used for palliation involves giving 40 Gy photon and 10 Gy neutron doses (14 MeV). Initiation of pain relief seems to occur faster with neutrons than with photons alone. Pain relief was achieved in 11 of 15 patients (73%), and the probability for a pain-free period is 46% for 9 months. It remains to be proven if the frequency of pain relief is higher and the pain-free period as well as the progression-free period last longer than with photons. The incidence of acute toxicity was 30% and late toxicity 10%. All toxicity was seen at the skin. A higher neutron dose will give better results, but may cause local radiation side-effects.

Carbon ion therapy offers the potential advantages of improved dose localization and enhanced biological effect [19]. Our results have shown that carbon ion therapy has the promising potential of delivering a sufficient dose to the tumor with acceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to carbon ions include locally advanced tumors with a non-squamous histology such as adenocarcinoma [20,21]. Carbon ion therapy may very well improve tumor control of recurrent rectal cancer.

In conclusion, carbon ion radiotherapy is an effective local treatment for patients with locally recurrent rectal cancer, and it seems to represent a promising alternative to surgery. The morbidity rate of carbon ion radiotherapy has so far been quite acceptable, although the long-term safety of this approach for patients with sarcomas will still need to be monitored.

References

[1] Kapiteijin E, Marijnen CAM, Colenbrander AC et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992. Eur J Surg Oncol 24:528-535, 1998

[2] Galandiuk S, Wieand HS, Moertel CG, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet 174: 27-32, 1992

[3] Bozzetti F, Mariani L, Micel R, et al. Cancer of the low and middle rectum: local and distant recurrence and survival in 350 radically resected patients. J Surg Oncol 62: 207-213, 1992
[4] Blakely EA, Ngo FQH, Curtis SB, et al. Heavy ion radiobiology: Cellular studies. Adv Radiat Biol 11:295-378, 1984
[5] Hall EJ. Radiobiology for the Radiologist. Philadelphia, PA, JB Lippincott, 1988, pp 281-291
[6] Sato K, Yamada H, Ogawa K, et al. Performance of HIMAC. Nuclear Physics A 588:229-234, 1995
[7] Kanai T, Endo M, Minohara S, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys 44:201-210, 1999
[8] Lopez-Kostner F, Fazio VW, Rybicki LA et al. Locally recurrent rectal cancer: Predictors and success of salvage surgery. Dis Colon Rectum 44: 173-178, 2001
[9] Wanebo HJ, Antoniuk P, Koness RJ et al. Pelvic resection of recurrent rectal cancer. Dis Colon Rectum 42: 1438-1448, 1999
[10] Ciatt S, Pacini P. Radiation therapy of recurrences of carcinoma of the rectum and sigmoid after surgery. Acta Radiol Oncolo 21: 105-109, 1082
[11] O'Connel MJ, Child DS, Moertel CG. A prospective controlled evaluation of combined pelvic radiotherapy and methanol extraction residue of BCG for locally unresectable or recurrent rectal cancer. Int J Radiat Oncol Biol Phys 8: 1115-1119, 1982
[12] Wong CS, Cummings BJ, Keane TJ. Combined radiation therapy, mitomycin C, and 5-Fluorouracil for locally recurrent rectal carcinoma. Int J Radiat Oncol Biol Phys 21: 1291-1296, 1991
[13] Lybeert MLM, Martijin H, DE NEVE W. Radiotherapy for locoregional relapses of rectal carcinoma after initial radical surgery. Int J Radiat Oncol Biol Phys 24:241-246,1992
[14] Knol HP, Hanssens J, Rutten HJT. Effect of radiation therapy alone or in combination with surgery and/or chemotherapy on tumor and symptom control of recurrent rectal cancer. Strahlenther Onkol 173: 43-49, 1997
[15] Murata T, Fujii I, Yoshino M. Radiation therapy with or without chemotherapy and hyperthermia for recurrent rectal cancer. J Jpn Soc Ther Radiol Oncol 9: 63-71, 1997
[16] Salo JC, Paty PB, Guillem J. Surgical salvage of recurrent rectal carcinoma after curative resection . Ann Surg Oncol 6: 171-177,1998
[17] Saito N, Koda K, Takiguchi N. Curative surgery for local pelvic recurrence of rectal cancer Dig Surg 20:192-200, 2002
[18] Moriya Y, Akasu T, Fujita S. Total pelvic exenteration with distal sacrectomy for fixes recurrent rectal cancer in the pelvis. Dis Colon Rectum 47: 2047-2054,2004
[19] Melton GB, Paty PB, Boland PJ. Sacral resection for recurrent rectal cancer. Dis Colon Rectum 49: 1099-1107, 2006
[20] Wendling P, Manz R, Thews G, et al. Heterogeneous oxygenation of rectal carcinomas in humans. Advances in Experimental Medicine & Biology 180: 293-300, 1984
[21] Hockel M, Schlenger K, Hockel S. Tumor hypoxia in pelvic recurrences of cervical cancer. Int J Cancer 79, 365-369, 1998
[22] Eising E, Potter R, Haverkamp U. Neutron therapy for recurrence of rectal cancer Strahlenther. Onkol 166: 90-94, 1990
[23] Ando K, Koike S, Ohira C, et al. Accelerated reoxygenation of a murine fibrosarcoma after carbon-ion radiation. Int J Radiat Biol 75: 505-512, 1999
[24] Kamada T, Tsujii H, Tsuji H, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. J Clin Oncol 20: 4466-4471, 2002
[25] Miyamoto T, Yamamoto N, Nishimura H, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 66: 127-140, 2003

Pancreas Cancer

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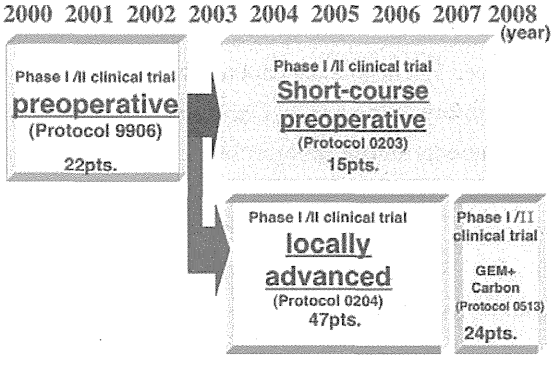
Abstract

Adenocarcinoma of the pancreas continues to be a significant source of cancer mortality in Japan, resulting in approximately 19,000 deaths a year. It is the fifth leading cause of cancer-related deaths in Japan, with a less than 5% 5-year expected survival rate[1]. About 70-75% of patients with pancreas cancer present with locally advanced disease or distant metastases and have a median survival time of only 6 months. For unresectable pancreas cancer, the median survival time with external beam radiation (EBRT) was better than with surgical bypass[2] or stents alone[3]. The median survival OF EBRT alone was 4 to 7 months[4]. The median survival with combined EBRT and chemotherapy for locally unresectable tumor was 8 to 10 months[5], better than with EBRT alone.

Local failure of these combined therapies was still 26 to 48%. On the other hand, surgery with curative intent is undertaken in 15-20% of patients. Even after resection, the predicted 5-year survival rates are still less than 20%[1]. Local recurrence in the pancreatic bed is seen in 50% of the patients undergoing presumed curative resection[6].

We examined the effect of carbon ion therapy in terms of reducing the rate of local recurrence in patients with locally advanced adenocarcinoma of the pancreas or undergoing resection for adenocarcinoma of the pancreas.

Fig.1 NIRS Sequencing Trial: Schema



・Carbon ion therapy (Fig.1)

A Phase I/II Clinical Trial of Carbon-ion Therapy for patients with preoperative pancreas cancer (9906) was carried out on surgically resectable patients from June 2000 through February 2003. This was followed by a Phase I/II Clinical Trial of Short-course Carbon-ion Therapy for patients with preoperative pancreas cancer (0203), commencing in April 2003 for similarly surgically resectable patients, with a fractionation regimen from 16 (4 weeks) to 8 (2 weeks) fractions. Concurrently, a Phase I/II Clinical Trial of Carbon-ion Therapy for patients with locally advanced pancreas cancer (0204) was conducted for surgically non-resectable patients with local progressive disease without distant metastasis from April 2003 through February 2007. This was followed by a Phase I/II Clinical Trial of Gemcitabine Combined with Carbon-ion Therapy for patients with locally advanced pancreas cancer.

A. Preoperative pancreas cancer (Protocol 9906, 16 fractions/4 weeks)

Purpose: We examined the effect of preoperative carbon ion therapy in terms of reducing the rate of local recurrence in patients undergoing resection for adenocarcinoma of the pancreas.

Patients and Methods: Twenty-two patients were enrolled into this trial. Median age was 63 years. Carbon ion therapy was given once daily, 4 days a week, for a fixed 16 fractions in 4 weeks. The dose was set at 44.8 GyE and escalated to 48.0 GyE at 5% increments.

Results: All patients completed the scheduled treatment course. Three grade 3 acute reactions and two grade 3 late reactions occurred among 16 of the patients treated with a total dose of 48.0 GyE. The two grade 3 late reactions were estimated to be caused by carbon ion therapy. Of the 22 patients, 15 (68%) had resection. All tumor specimens pathologically revealed evidence of grade 2 treatment effects with significant fibrosis, hyalinization, and necrosis (pathological grade 2 is defined as less than 33% active cancer cells). Remarkable antitumor effects were observed. The overall local control rates were 100% and 87% at 1 year and 2 years of follow-up, respectively. No local failure was observed in any of the 22 enrolled patients.

Conclusion: Carbon ion radiotherapy seems to be a safe and effective modality in the management of resectable pancreatic carcinoma, providing good local control and offering a survival advantage without unacceptable morbidity.

Patients and Methods

Patient Eligibility

Between April 2000 and February 2003, 22 patients judged according to the staging criteria of the Japanese Committee on Cancer as being at clinical stages I, II, III or IVa, equivalent stages I, II or III by the TNM staging criteria, were enrolled into this trial. Criteria for trial eligibility were pathologic confirmation of ductal adenocarcinoma, age of 18 years or more, ECOG performance score 0, 1, or 2, and adequate hematologic, hepatic, renal, and cardiopulmonary function to allow pancreatectomy. Exclusion criteria were having another primary tumor and infection at the tumor site. Patients who had undergone chemotherapy before carbon ion radiotherapy or those who had prior radiation therapy at the same site were excluded from the study. The tumor had to be grossly measurable, but its size could not exceed 15 cm, and the patients were evaluated by surgical consultation with three surgical investigators as to the resectability of the lesion. Chest and upper abdominal CT scans were mandatory at the time of entry into the trial. All patients signed an informed consent form approved by the local institutional review board.

Carbon Ion Radiotherapy

The features of the accelerator and the carbon ion beam have previously been described[7,8].

Carbon ion therapy was given once daily, 4 days a week, for a fixed 16 fractions over 4 weeks. The dose was set at 44.8 GyE and escalated to 48.0 GyE at 5% increments. The protocol specifications for carbon ion radiotherapy were as follows. The target volumes were established by CT scan. Field arrangements were generally designed using a 3-field or 4-field plan. The clinical target volume (CTV) included the gross tumor volume (GTV) and regional lymph nodes, which included the celiac, superior mesenteric, peri-pancreatic, portal and para-aortic (celiac-IMA) nodes for pancreatic head cancer and splenic nodes for pancreatic body and tail cancer. The CTV was defined as the gross volume plus 1.0 cm or 0.5 cm (in contact with the gut). At least 50% of the functioning renal parenchyma was limited to 15 GyE or less. The spinal cord dose was limited to 30 GyE or less.

Surgery

Surgical resection was to be performed 2 to 4 weeks after the completion of carbon ion radiotherapy if there was no disease progression to an unresectable status as determined by repeated abdominal CT scans, a prohibitive decline in performance status, or other evidence of metastatic disease. Median time from the last day of carbon ion radiotherapy to surgical resection was 21 days (range, 20 - 26 days).

Tumor Response and Local Control Criteria

Tumor response was defined as the maximum tumor response observed by the RECIST scoring system during the first 6 months after the initiation of carbon ion radiotherapy. Complete response (CR) was defined as the disappearance of all measurable tumor in the treatment volume. Partial response (PR) meant a 30% or greater decrease in tumor size (longest diameter). Stable disease was that with a less than 30% decrease or a less than 20% increase in tumor size. Progressive disease was defined as a 20% or greater increase in tumor size. Local recurrence was defined in terms of lesions occurring in the treatment volume based on CT, MRI, and PET scans. The development of a new, low-density mass in the region of the pancreatic bed was considered evidence of local recurrence even in the absence of symptoms, and cytologic or histologic confirmation of recurrent disease was not required. The absence of local recurrence was described as local control.

Histologic evaluation of the effects of carbon ion therapy included assessment of cytologic changes in conjunction with quantification of the amount of viable residual carcinoma cells (Table 1). Upon completion of specimen analysis, all cases were reviewed by the same histopathologist.

Table 1. Grading system for radiation treatment effects

Grading system for radiation treatment effects

Grade	Histological appearance
0	No tumor cell destruction evident
1	Less than two-thirds of tumor cells are destroyed
2	More than two-thirds of tumor cells are destroyed
3	No viable tumor cells present

Statistics

Survival time and local control time were defined as the interval between the initiation of carbon ion radiotherapy and the date of death or the date of diagnosis of local failure, respectively.

Results

Patient Characteristics

None of the 22 patients initially registered into this trial was excluded from the analysis. The patients consisted of 14 males and 8 females. Median age was 63 years (range, 42 - 77 years). Thirty cancers originated in the head of the pancreas, 8 were in the body of the pancreas, and one was in both the head and body (Table 2).

Table 2. Patient Characteristics

Characteristics		Number of patients (%)
Age (years)	median (range)	22 (42-77)
Gender	male	14
	female	8
ECOG performance score	0	18
	1	4
Tumor location	head	13
	body-tail	8
	head and body	1
Tumor size by CT (mm)		
Stage (preoperative, TNM))		
T3N0		4
T3N1		18

Toxicity

The toxicities in the 22 patients receiving carbon ion therapy are listed in Table 3. The toxicities were relatively few and mild. All patients completed the scheduled treatment course. Three grade 3 acute reactions and two grade 3 late reactions occurred among 12 of the patients treated with a dose of 48.0 GyE. One patient had cholangitis, easily resolved by radiologic stent change and antimicrobials. Two were postoperative complications: one patient had leakage at the choledochojejunostomy, requiring percutaneous drainage, and the other had gastrojejunostomy leakage, requiring percutaneous drainage. Both leakages occurred outside of the treatment fields and were considered to likely not be related to the carbon ion therapy. There was no grade 3 to 5 blood or bone marrow reaction. Both two grade 3 late reactions were post-surgery portal vein stenoses, and both underwent portal vein resections.

Table 3. Acute and Late Toxicities by NCI-CTC and RTOG/EORTC Scoring System

	Acute (NCI-CTC)						Late (RTOG/EORTC)					
	No. of patients	Gr0	Gr1	Gr2	Gr3	Gr4	No. of patients	Gr0	Gr1	Gr2	Gr3	Gr4
Skin	22	22	0	0	0	0	20	20	0	0	0	0
Gastrointestinal	22	18	3	1	0	0	20	20	0	0	0	0
Bile duct	22	20	0	1	1	0	20	20	0	0	0	0
Portal vein	22	20	0	2	0	0	20	18	0	0	2	0
Leakage	22	20	0	0	2	0	20	20	0	0	0	0

Tumor Response

Evaluation of tumor response was not considered the primary endpoint of this study.

All 22 patients had CT scans before registration and 2-4 weeks after completion of the carbon ion radiotherapy. On the basis of the CT scans, only one patient showed complete response, and one also showed partial response. Twenty patients (91%) had stable disease, but none had local tumor progression.

Surgical Results

Of 22 patients, 15 (68%) had resection. One of the 22 eligible patients did not undergo surgery. CT scan restaging after carbon ion radiotherapy revealed new liver metastases in this patient. Of the 21 patients undergoing exploratory celiotomy, 5 had no resection. Two had metastases to the liver and three to the peritoneum. Fifteen eligible patients had pancreatic resection; 10 modified Child procedures, two total pancreatectomies, and three distal pancreatectomies were performed. In addition, one patient also underwent solitary liver resection for a small isolated liver metastasis discovered intraoperatively after pancreaticoduodenectomy. This patient, who had pancreatectomy that was not considered potentially curative resection, was included in this analysis. The median time from completion of carbon ion radiotherapy to surgery was 22 days (range, 13 - 29).

Pathological Results of Resected Specimens

The pathological characteristics of the 15 resected specimens are listed in Table 3. All tumor specimens revealed evidence of grade 2 treatment effects with significant fibrosis, hyalinization and necrosis, meaning more than two-thirds of the tumor cells were destroyed. The resection margins were examined in all specimens. No patient had a grossly or microscopically positive resection margin.

Table 4. Pathological results of the 15 resected specimens

Total dose (GyE)	No. of patients	Grade0	Grade1	Grade2	Grade3
44. 8	5	0	0	5	0
48. 0	10	0	0	10	0

Patient Outcome

The overall local control rates were 100% at 1 year and 87% at 2 years of follow-up, respectively. One local failure was observed in the residual pancreas at 18 months after pancreaticoduodenectomy. There was no local and regional recurrence within the treatment fields. The 1-year overall survival rates were 62% for all patients and 90% in the resected patients, and median survivals were 13.4 months and 21 months, respectively, with a median follow-up of 13 months (range, 3.3 - 51 months) (Fig.2). Two patients are currently alive without evidence of disease. Twenty patients are dead and 19 patients had metastatic relapse or carcinomatosis. In the nonresected patients, the 1-year overall survival rate and median survival were 30% and 6.3 months. This level of survival rate achieved with carbon ion RT alone can be considered as equivalent to chemoradiation(table5).

Fig.2 Overall survival for all 22 patients and the resected patients

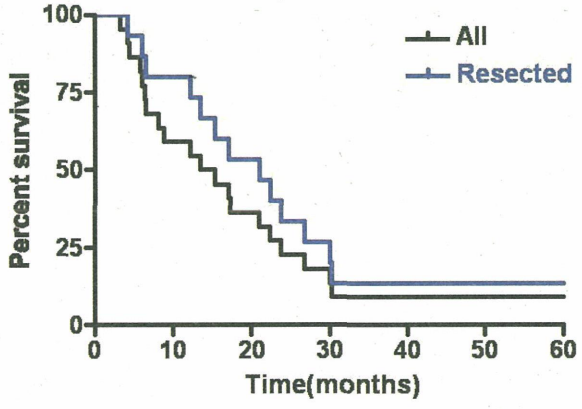


Table 5. Results on the Preoperative Radkliotherapy for Resected Pancreatic Cancer

Author	year	No	EBRT DOSE	Chemo	Median	1-y Surv.	Local Failure
Staley CA	1996[7]	39	50.4	5FU	19	81%	11%
Hoffman JP	1998[8]	24	50.4	5FU	15.7	71	13
Pister PWT	2002[9]	20	30	PAC	19	75	
Maginin V	2003[10]	19	50.4	5FU	30	81	
NIRS	2010	14	44.8-48.0	-	21	86	0

B. Short-course (8 fractions/2 weeks) preoperative pancreas cancer (Protocol 0203)

The phase I/II trial of preoperative carbon ion radiotherapy (8 fractions/2 weeks) for pancreas cancer prior to surgery was performed with the purpose of establishing the safety of carbon ion radiotherapy, determining the recommended dose, and substantiating its preoperative effectiveness.

At present, we are trying to give 36.8GyE of carbon ions, patient enrollment in the trial is in progress, and the outcomes are pending. The early data indicate the same high level of local control as the 9906 protocol. However, the histological effect is showing a tendency of being somewhat inferior to the 9906 protocol, suggesting that the dose is not adequate. The 3-year overall survival rates were 30% for all patients and 51% in the resected patients. In view of the reports in the literature on drugs with a sensitizing effect in conjunction with heavy particle beams, further studies are scheduled in search for an even more effective treatment modality.

C. Locally advanced pancreas cancer (Protocol 0204, 12 fractions/3 weeks)

The phase I/II trial of carbon ion radiotherapy (12 fractions/3 weeks) for locally advanced pancreas cancer was performed so as to establish the safety of carbon ion radiotherapy, determine the recommended dose, and confirm its efficacy.

Patients and Methods

Between April 2003 and February 2007, 47 patients judged according to the staging criteria of the Japanese Committee on Cancer as being clinical stages IVa or IVb without distant metastasis were enrolled into thi trial. As one patient was excluded because of receiving chemotherapy before treatment, 46 patients were eligible for this analysis. Patients eligible for study entry had been histologically or cytologically confirmed with locally advanced unresectable pancreas ductal carcinoma. Eligibility criteria were: confirmation of ductal carcinoma by CT findings, age of 80 years or younger, ECOG performance score 0, 1, or 2, and hepatic, renal and cardiopulmonary function sufficient for undergoing surgery. The criteria of the CT findings for non-resectability of the tumor included tumor encasement of the celiac trunk and/or superior mesenteric artery. Carbon ion therapy was given once daily, 4 days a week, for a fixed 12 fractions over 3 weeks. The dose was set at 38.4 GyE and escalated to 52.8 GyE at 5% increments.

Results

Toxicity on organs such as skin, bladder and digestive tract was assessed according to the NCI-CTC (acute) and RTOG/EOTRC (late) classifications. Tumor response was defined by the RECIST scoring system as the maximum tumor response observed during the first 6 months after the initiation of carbon ion radiotherapy. Local recurrence was defined in terms of lesions occurring in the tumor bed.

Survival was calculated as the time from the initiation of carbon ion therapy until death. Survival curves were estimated by the Kaplan-Meier method.

All toxicities in the 46 patients receiving carbon ion therapy are listed in Table 8. All patients completed the scheduled treatment course. Seven grade 3 acute and one grade 3 late toxicities were observed. Six of the 7 grade 3 acute toxicities were anorexia and one was cholangitis. Tumor response was evaluated in 46 lesions. CR was observed in one lesion, PR in 7, SD in 37, and PD in one. The local control rate at 1 year in the 46 analyzed patients and in the patients receiving 45.6 GyE or more was 76% and 95%, respectively (Fig.3). The overall survival estimates for the 46 analyzed patients and the patients receiving 45.6 GyE are shown in Fig. 4. One-year overall survival was 43%.

Fig.3 Local control rates for all 46 patients by total dose

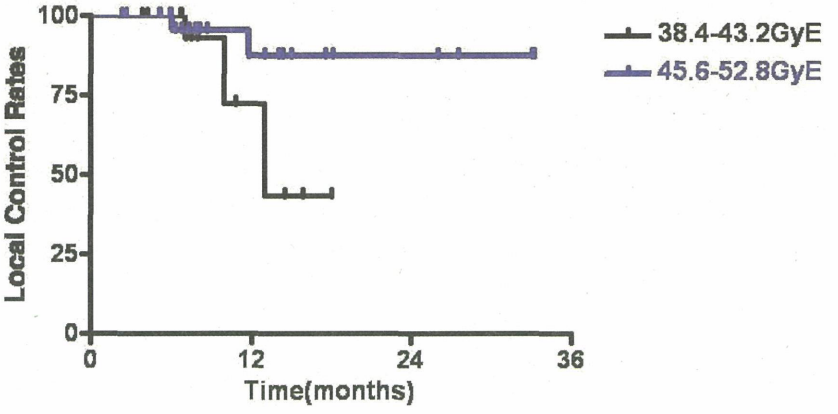
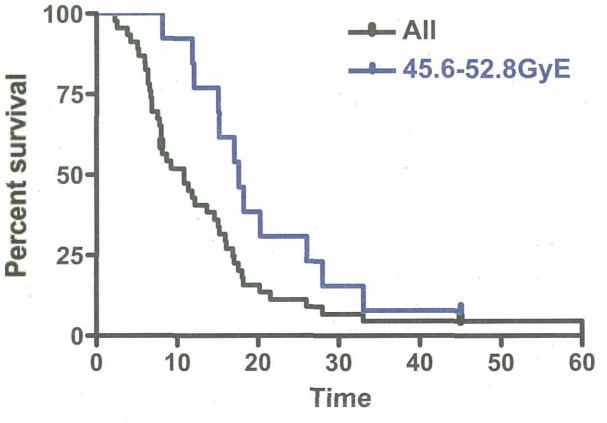


Fig.4 Overall survival for all 46 patients and the higher dose group



The maximum acute reaction of grade 3 was observed in two-thirds of the patients (67%) at 52.8 GyE. From these results, we concluded that the maximum tolerance dose of carbon ions is 52.8 GyE/12 fractions/3 weeks.

On the basis of the literature on drugs with a sensitizing effect in conjunction with heavy particle beams, further studies were scheduled in an effort to find even more effective treatment modalities based on a combination of chemo- and radiotherapy. We started a Phase I/II Clinical Trial of Gemcitabine Combined with Carbon-ion Therapy for patients with local advanced pancreas cancer from April 2007.

D Gemcitabine Combined with Carbon-ion Therapy (Protocol 0513, 12 fractions/3 weeks)

From the results of the 0204 clinical study, carbon ion radiotherapy considerably improved tumor control of locally advanced pancreas cancer with acceptable morbidity in the surrounding normal tissues, but sufficient survival benefit could not be achieved. On the basis of the literature on drugs with a sensitizing effect in conjunction with heavy particle beams, further studies were scheduled in an effort to find even more effective treatment modalities based on a combination of chemo- and radiotherapy. We started a Phase I/II Clinical Trial of Gemcitabine Combined with Carbon-ion Therapy for patients with locally advanced pancreas cancer from April 2007.

The dose escalation schedule of Gemcitabine combined with carbon ion radiotherapy is shown in Fig.5. First the dose of carbon ion radiation was fixed at 43.2 GyE and the dose of gemcitabine was escalated from 400 mg to 1000 mg; then the dose of gemcitabine was fixed at 1000 mg and the dose of carbon ion radiation was escalated from 45.6 Gye to 50.4 GyE. Carbon ion therapy was given once daily, 4 days a week, for a fixed 12 fractions over 3 weeks. Gemcitabine was given once weekly (Fig.6).

At present we are trying to give 1000 mg/m^2 combined with 48.0 GyE of carbon ions. All patients completed the scheduled treatment course. This trial is still ongoing. Gemcitabine combined with carbon ion radiotherapy may be well tolerated by patients with pancreas cancer. The 1-year overall survival rates were 82% for 12 patients given 1000 mg/m^2 combined with 43.2 GyE of carbon ions.

Fig 5. Dose Escalation Schedule (0513)

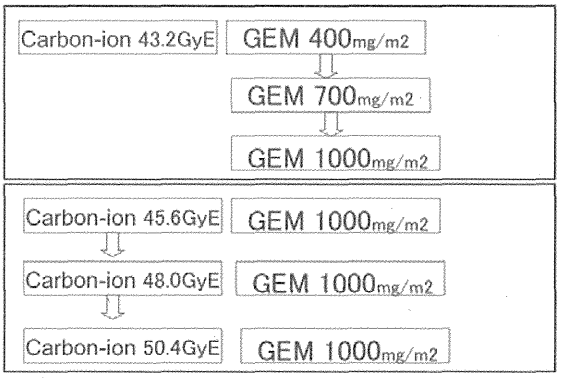
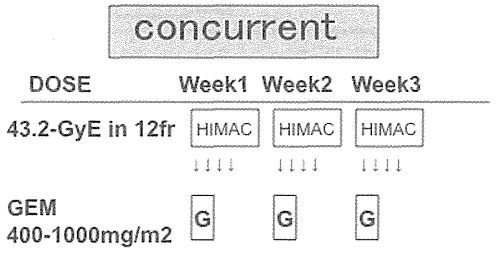


Fig.6 Treatment schema for combination Of Gemcitabine and Carbon-ion Therapy



Reference

[1] Registration committee of pancreatic cancer. Annual Report of Nationwide Survey of Pancreatic Cancer. J of Jpn Panc Surg. 18: 101-169, 2003

[2] Lillemoe KD, Cameron JL, Hardacre JM et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? Ann Surg. 230: 322-330, 1999

[3] Prat F, Chapat O, Ducot B et al. A randomized trial of endoscopic drainage methods for inoperable malignant stricture of the common bile duct. Gastrointest Endosc. 47: 1-7, 1998

[4] Roldan GE, Gunderson LL, Nagorney DM et al. External beam versus intraoperative and extrabeam irradiation for locally advanced pancreatic cancer: Cancer. 61:1110-1116, 1988

[5] Moertel CG, Gundeson LL, Mailliard JA et al. Early evaluation of combined fluorouracil and leucovorin as a radiation enhancer for locally unresectable, residual, or recurrent gastrointestinal carcinoma. J Clin Oncol. 12:21-27, 1994

[6] Griffin JF, Smalley SR, Jewell W et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer. 66: 56-61, 1990

[7] Staley CA, Lee JE, Cleary KR et al. Preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for adenocarcinoma of the pancreas head. Am J Surg 171:118-126,1996

[8] Hoffman JP, Lipsitz S, Pisansky T. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas. J Clin Oncol 16: 317-323, 1998

[9] Pisters PWT, Janjan WNA, Cleary KR. Preoperative paclitaxiel and concurrent rapid-fraction radiation for resectable pancreas adenocarcinoma. J Clin Oncol 20:2537-2544, 2002

[10] Magnin M, Mountardier V, Giovannini MH, Neoadjuvant preoperative chemoradiation in patients with pancreatic cancer. Int J Radiation Oncology Biol Phys 55: 1300-1304, 2003

[11] Sato K, Yamada H, Ogawa K, et al. Performance of HIMAC. Nuclear Physics A. 588:229-234, 1995

[12] Kanai T, Endo M, Minohara S, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys. 44:201-210, 1999

Carbon Ion Radiotherapy for Prostate Cancer

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Abstract

Purpose: Analysis on the results of hypofractionated conformal carbon ion radiotherapy (C-ion RT) for localized prostate cancer was performed, with regard to normal tissue morbidity, biochemical relapse-free rate (bNED), and patient survival. Methods and Materials: Eight hundreds and eighteen prostate cancer patients who received C-ion RT established through two preceded dose-escalation studies were analyzed in regard to toxicity, survival, and bNED. Results: Concerning radiation morbidity, no grade 3 or higher toxicities were observed either in the rectum or genitourinary system (GU), and the incidences of grade 2 rectum and GU morbidity were only 1.9% and 5.8%, respectively. Incidence of late toxicity in the patients treated with C-ion RT of 16 fractions was lower than that of 20 fractions. Overall bNED at 5 years was 90.1%, with only five local recurrences. The bNED of the C-ion RT of 16 fractions was comparable to that of 20 fractions. Gleason's score, T-stage, and initial PSA were significant prognostic factors for bNED, and T-stage and initial PSA were also significant prognostic factors for overall survival rate. C-ion RT with the established dose fractionation regimen yielded satisfactory bNED with very few local recurrences, and with minimal morbidity. C-ion RT of 16 fractions could offer even lower incidence of GU toxicity than that of 20 fractions, without deteriorating the biochemical control.

Introduction

Prostate cancer is a slow-growing tumor occurring in advanced-age male patients, but the incidence and mortality rate are both rapidly increasing in Asian as well as in Western countries. Radiotherapy is one of the treatments of choice for localized or locally advanced tumor of the prostate. In order to obtain satisfactory results, sufficient radiation effect with desirable dose concentration is required. This tumor is relatively radio-resistant, and severe damage to adjacent normal tissues will have deleterious effects on the quality of life after the treatment.

Carbon ion radiotherapy (C-ion RT) may be the ideal radiation treatment for prostate cancer because of the unique physical and biological advantages of carbon ion beams (1). The successful results obtained with novel conformal radiotherapy techniques, such as three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) (2-4), are evidence that dose conformity confers clear advantages to the radiotherapy of prostate cancer. Carbon ion beams offer superior dose conformity in the treatment of deep-seated tumors compared to the state-of the-art techniques of X-ray therapy, and therefore C-ion RT possesses a greater potential of further improving the treatment outcome of prostate cancer (1).

In this respect, high-linear energy transfer (LET) radiation therapy with fast neutrons was found to yield an excellent tumor control rate. Its unacceptably high toxicity (5,6), however, has stood in the way of this therapy coming into wider use. The high incidence of morbidity associated with fast neutron therapy was mainly due to

an inferior dose concentration of neutron beams. This problem, however, can be solved by the use of heavy charged particle beams, such as carbon ions, without foregoing the radiobiological advantages of high LET radiation.

To establish an appropriate dose fractionation regimen for C-ion RT, two phase I/II clinical studies have been performed (7-9) at the National Institute of Radiological Sciences, Chiba, Japan (NIRS) 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 (10,11). 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 (9-11). This article presents the methods and updated outcomes of this established C-ion RT, and also describes its future prospects at NIRS.

Materials and Methods

1. Protocols

So far, a total of 1,004 patients have been enrolled, 97 patients in the first two phase I/II studies, 176 in the phase II study, and 731 after official approval for the application of the procedure as a highly advanced medical technology (Table 1). Of this total, 818 patients received the established treatment of C-ion RT, and were followed up for at least 6 months and analyzed.

Table1. Clinical studies of C-ion RT for prostate cancer at NIRS

Protocol	Study Design	T-stage	Period	Total Dose (Gy RBE/f)	Hormone therapy	Number of patients
9402	Phase I / II Dose escalation	T2b~T3	95.6～ 97.12	54.0～ 72.0/20	(+)	35
9703	Phase I / II					
	Dose escalation	T1~T2a	98.1～ 00.2	60.0～ 66.0/20	(-)	20
	Fixed dose	T2b~T3		66.0/20	(+)	42
9904	Phase II Fixed dose	T1~T3	00.4～ 03.11	66.0/20	High*(+) Low* (-)	176
		T1~T3	03.12~ 09.8	66.0, 63.0/20 57.6/16	High* >24m Interm* =6m Low* (-)	731
Total			95.6 ～ 09.8			1,004

*Stratified by risk factors; Clinical stage, initial PSA, and Gleason score

Patients were eligible if they had histologically proven prostatic adenocarcinoma, that is, stage T1, T2 or T3 primary tumors (12) without radiologically detectable distant metastasis (M0), involvement of regional lymph nodes (N0, pN0), or solitary, non-fixed involvement of regional lymph nodes diagnosed by staging pelvic lymphadenectomy (pN1). Eligible patients were required not to have undergone previous treatment for prostate cancer except for hormone therapy. All patients signed an informed consent form approved by the local institutional review board. Pathological specimens were reviewed centrally before registration, and those of the phase I/II studies were reviewed retrospectively.

Until September 2005, patients were stratified into two subgroups, high-risk and low-risk groups according to T-staging, Gleason's score (GS), and initial serum PSA. Thereafter, the high-risk group was further divided into two groups — an intermediate-risk group and a true high-risk group. For the true high-risk group patients, namely, patients with T3 primary tumor, GS ≥ 8 or a serum PSA value ≥ 20 ng/ml, long-term (≥ 24 months) hormonal therapy was applied in combination with C-ion RT. Patients in the low-risk group, that is, T1/T2a patients with GS < 7 and serum PSA < 20 ng/ml, received only C-ion RT. For the intermediate-risk group patients, consisting of those with a serum PSA value < 20 ng/ml and T2b primary tumor or GS of 7, combined treatment of C-ion RT and short-course (6 months) hormonal therapy was performed (Fig.1).

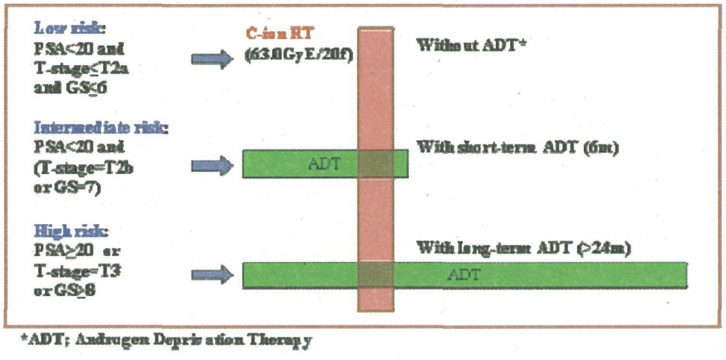

Fig. 1. Current treatment strategy for prostate cancer at NIRS

Patients were divided into three risk groups of high, intermediate, and low, according to their T-stage, nitial PSA, and Gleason score.

2. Carbon Ion Radiotherapy

1) Treatment techniques

In order to make good use of excellent dose concentration of carbon ion beam, some techniques were developed for keeping high precision and sufficient reproducibility in the patient positioning and field placement. Techniques we applied were;

a) Rigid immobilization

b) Volume control of the rectum and the bladder

c) Precise field-localization with bony structure

a) Rigid immobilization

The feet and head of patients were positioned in the customized cradles (Moldcare; Alcare, Tokyo, Japan) and the pelvis was immobilized with a low-temperature thermoplastic of 3 mm thickness (Shellfitter; Keraray Co, Ltd, Osaka, Japan), which can give mild pressure on the lower abdominal wall and reduce organ motion in the pelvis. With this method of immobilization, intra-fractional motion of the prostate was evaluated less than 2 mm .

b) Volume control of the rectum and the bladder

Bladder was filled with 100ml of sterilized water both at the time of CT acquisition and at each treatment session in the case of beam irradiation in the vertical direction. The patient was instructed to empty the rectum as much as possible just before the treatment and a laxative or enema was used, if necessary. Amount of gas in the rectum was carefully observed by positioning images and the set-up was repeated in case necessary.

c) Precise field-localization with bony structure

At every treatment session, the patient's position was verified with a computer-aided, on-line positioning system. The patient was positioned on the treatment couch with the immobilization devices, and digital orthogonal x-ray television images were taken in that position and transferred to the positioning computer. The positioning images were compared with reference images, which were checked to confirm their match with the

digitally reconstructed radiograph (DRR). Any differences, if found to exist, were measured. The treatment couch was then moved to the matching position until the largest deviation of all points was less than 2mm.

2) Treatment Planning

A set of 2.5-mm-thick CT images was taken for treatment planning, with the patient placed in immobilization devices. Three-dimensional treatment planning was performed using HIPLAN software (National Institute of Radiological Sciences, Chiba, Japan) (13). 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.

C-ion RT was given once a day, 4 days a week. One port was used in each session. Patients were treated from 5 irregularly shaped ports, one anterior-posterior port and a pair of lateral ports for the PTV-1 and another pair of lateral ports for the PTV-2. A hundred % of the prescribed dose was given at the maximum dose point of each portal. The PTV-2 was covered by at least 90% of the prescribed dose and the minimum dose of the PTV-1 was more than 50% of the maximum dose and depended on the volume spared by PTV-2.

Dose was expressed in Gray-Equivalent (GyE = physical carbon ion dose (Gy) x Relative Biological Effectiveness {RBE}). Irrespective of the size of the Spread-Out Bragg Peak (SOBP), the RBE value for carbon ions was estimated to be =3.0 at the distal part of the SOBP. The compensation bolus was fabricated for each patient to make the distal configuration of the SOBP similar to the PTV. The multi-leaf collimator or the customized brass collimator defined the margins of the PTV. Fig. 2 shows the representative dose distribution.

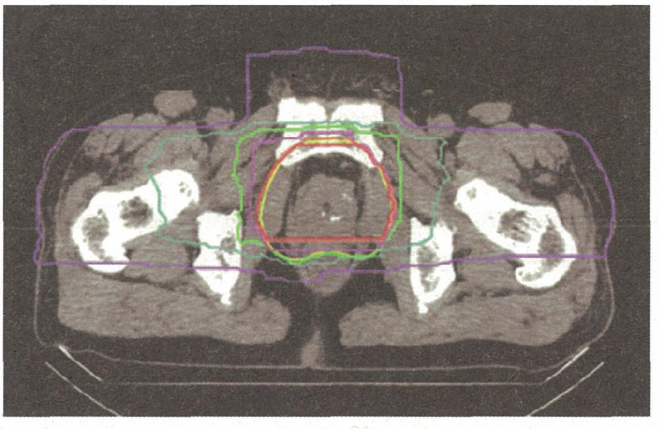

Fig.2. Typical dose distribution of carbon ion radiotherapy

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 (11). In addition, more hypofractionated schedule of 57.6GyE/16fractionas was applied since September 2007. This newly applied fractionation had been tested in the other patients group who could not enrolled to the clinical studies because of the prolonged neoadjuvant hormonal therapy since April 2003.

3. Androgen Deprivation Therapy (ADT)

Before C-ion RT, neoadjuvant androgen deprivation therapy (ADT) such as medical or surgical castration with or without antiandrogen was applied for 2 to 6 months to the patients of the high-risk and intermediate-risk groups. Adjuvant ADT was continued for a duration of 6 months for the intermediate-risk patients and for more than 24 months for the high-risk patients. The median duration of ADT of 690 patients receiving combined treatment was 24.1 months. The remaining 128 patients received C-ion RT only.

Results

Of the 818 analyzed patients, 469 (57.3%) were categorized as high-risk, 206 (25.2%) as intermediate-risk, and 143 (17.5%) as low-risk according to our definition of risk grouping. The average pretreatment PSA value was 26.1 ng/ml, with a median of 13.6 ng/ml and a range of 3.4 - 810.0 ng/ml. Two hundreds and ninety three (35.8%) patients had an initial PSA value of more than or equal to 20 ng/ml. Two hundreds and seventy (33.0%) patients had T3 primary tumors and the remaining 548 (67.0%) had T1 or T2 tumors. Two hundreds and one (24.7%) patients had GS of less than, or equal to 6, 381 (46.9%) had GS of 7, and 231 (28.4%) had GS of more than, or equal to 8. Median follow-up period was 35.8 months at the time of analysis.

1. Toxicity

The cumulative incidence of late rectum and genitourinary morbidities in the 740 patients treated with either of 20 fractions or 16 fractions and followed up more than 12 months are summarized in Table 2. None of the patients had developed grade 3 or higher morbidities up to the latest follow-up. Grade 2 morbidities of the genitourinary system and rectum were observed in 5.8% and 1.9% of the patients, respectively. Regarding the effect of alteration in dose fractionation, both the rectal and GU toxicity in 57.6.GyE/16f were a substantially less frequent than those in 66.0GyE/20f or 63.0GyE/20f.

Table 2. 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
66.0/20	250	196	46	8	0	103	121	26	0
	(%)	(78.4)	(18.4)	(3.2)	(0)	(41.2)	(48.4)	(10.4)	(0)
63.0/20	216	188	24	4	0	112	94	10	0
	(%)	(87.0)	(11.1)	(1.9)	(0)	(51.9)	(43.5)	(4.6)	(0)
57.6/16	274	252	20	2	0	156	111	7	0
	(%)	(92.0)	(7.3)	(0.7)	(0)	(56.9)	(40.5)	(2.6)	(0)
Total	740	636	90	14	0	371	326	43	0
	(%)	(85.9)	(12.2)	(1.9)	(0)	(50.1)	(44.1)	(5.8)	(0)

2. Survival and Tumor Control

The Kaplan-Meier estimates of overall and biochemical relapse free (bNED) survivals for the 818 patients at five years were 95.6% and 90.1%, respectively (Fig.3). By the date of analysis, 24 patients had died, 6 of metastasis from the prostate, and 18 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 five patients, three presenting with slowly elevated PSA and positive biopsies at 24 months, 38 months, and 48 months after C-ion RT, and two with apparent growth of tumor on the MRI images, were judged as having local recurrence. By the date of analysis, 48 patients met the Phoenix criteria of biochemical failure: more than 2.0 ng/ml rise of PSA from the nadir. Of these 48 patients, 23 patients were diagnosed as having metastasis – 11 in bone and 12 in pparaaortic or pelvic lymph nodes – 2 to 62 months after biochemical relapse, 5 were judged as having local recurrence, and the remaining 20 patients had no clinical evidence of recurrent lesions at the date of analysis.

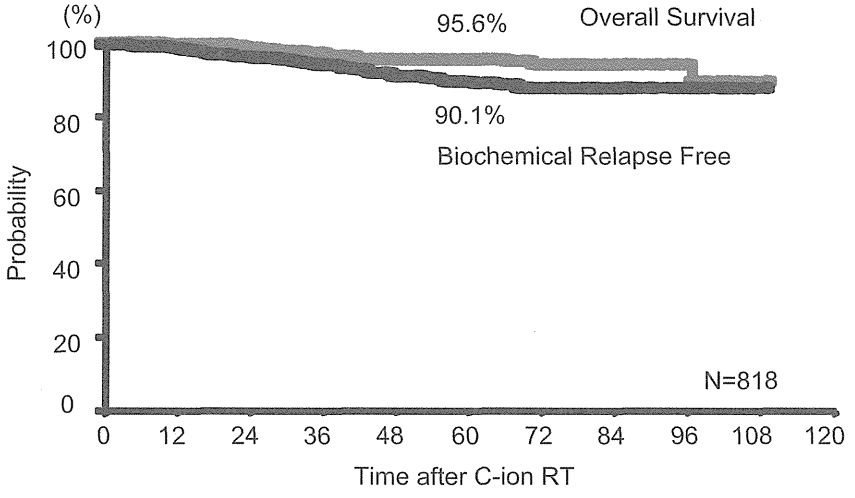

Fig. 3. Overall and biochemical relapse free survival curves of all analyzed patients
Figure indicates 5-year rate of each curve.

3. Prognostic factors

Additional analysis was carried out to evaluate the influence of several prognostic factors on bNED and overall survival (OS), 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 lower bNED and OS. Five-year bNED and OS in T1/2 patients were significantly better than those in T3 patients. However, the 5-year bNED of 89.6% was remarkably high compared to other radiotherapy series for T3 patients.

The centrally reviewed GS also had significant influence on bNED, as 5-year bNED of the patient subgroup with GS ≥ 8 was significantly lower than those of the subgroups with GS ≤ 6 and GS = 7, though OS was not significantly different (Table 3).

Table 3. Biochemical relapse free rate (bNED) and overall survival rate (OS) according to risk factors

			5-year rates (%)			
		No.pts.	bNED	p-value	OS	p-value
All		590	90.4		94.7	
Stage	T1/2	487	94.1	0.0081	97.6	0.0129
	T3	103	83.2		89.6	
PSA	< 20	385	92.6	0.0531	95.5	0.0432
	20 ≤	205	87.0		91.5	
Gleason score	≤ 6	157	92.7	0.0109	96.1	
	7	260	94.7	0.0006	96.0	n.s.
	8 ≤	173	79.5		90.4	

Regarding the effect of altered fractionation on bNED, there was no difference among the patients treated in 20f and those in 16f (Fig. 4). On the basis of these results on bNED and toxicity, that is relatively low toxicity with comparable bNED in 16 fractions, we started to treat all new patients with a dose fractionation of 57.6GyE/16f in September 2007.

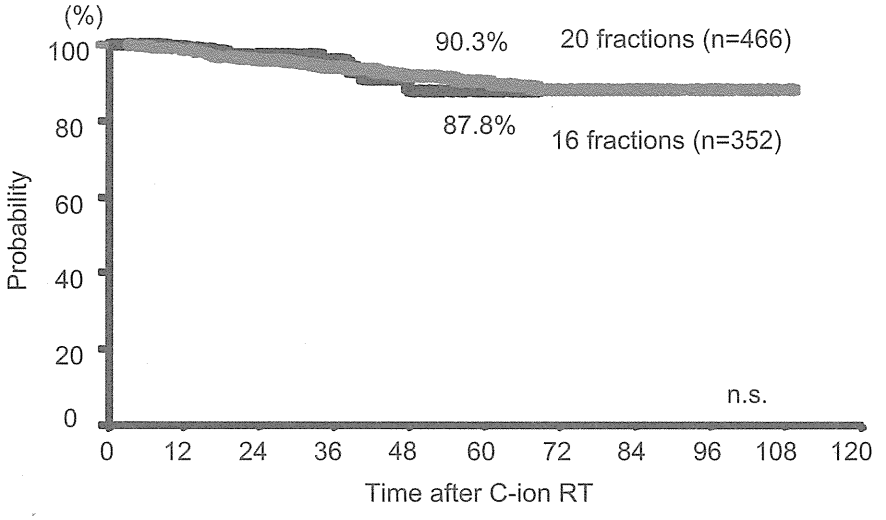

Fig. 4. bNED according to altered fractionation of carbon ion radiotherapy

Discussion

In this article, the prostate cancer patients treated with the carbon ion radiotherapy (C-ion RT) procedure established in our phase I/II clinical studies were analyzed. The results have demonstrated that C-ion RT achieves a very high biochemical control rate with a relatively low morbidity. A high rate of biochemical control was achieved as a result of the excellent dose concentration associated with C-ion RT and the efficient application of hormonal therapy. A number of studies using radiation therapy in combination with hormonal therapy have also indicated a high rate of biochemical control (13-14). Comparing our results with meta-analysis of the RTOG study, survival rates in all patient subgroups were even better than those of the combinations of hormone therapy and conventional photon radiotherapy (Table 4). We presume the higher survival rate to be due to the positive impact of carbon ion beams on local tumor control, even in the high-risk group patients.

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

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	66-63/20 or 57.6/16	263	99%	190	93%	176	87%

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

In photon radiotherapy, the rate of local recurrence can be affected by the actual volume or pathological differentiation of tumor tissue. However, high LET radiation can be expected to be more effective for large-volume, poorly differentiated tumors compared to photon irradiation, and, in fact, very few local recurrences

were actually observed in our series, even in the T3 tumor with a high GS. Substantially higher survival rate in very high-risk group (Group 4 in the Table 4) could be achieved only by substantially more effective treatment than conventional photon radiotherapy.

A very low incidence of rectum morbidity was recorded, and this is ascribable to the physical properties of heavy charged particles in terms of dose conformity. This also substantiates the validity of our methods of patient positioning and target setting, and of our irradiation techniques. In addition, the acceptable incidence of genitourinary morbidity and the very high efficacy against local tumors confirm the accuracy of our dose calculation, the biological advantage of carbon ion beams, and the effect of a relatively high dose by a hypofractionated schedule. Incidences of late radiation toxicities in various radiotherapies were summarized in Table 5. IMRT and Proton therapy could achieve lower incidence than 3DCRT, and C-ion RT, particularly of 57.6GyE/16f, could achieve even lower incidences both in the rectum and GU system.

A further move in the direction toward a more hypofractionated regimen of 16 fractions over 4 weeks has already been made. In 274 patients treated with a C-ion dose of 57.6 GyE in 16 fractions, bNED was comparable to that of 66.0GyE/20f or 63.0GyE/20f, and incidence of GU toxicity was even lower. Therefore, this new dose fractionation is applied to all new patients at the NIRS. Further, it is now planning to conduct the new clinical study with more hypofractionated C-ion RT of 51.6GyE/12f.

Table 5. Incidence of Late Radiation Toxicity in various radiotherapy for Prostate

Institutes	Radiotherapy	Dose(Gy/f)	No. of pts.	Morbidity [3] 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	1.9%	4.6%
	Carbon	57.6/16	274	0.7%	2.6%

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

Conclusions

In conclusion, carbon ion radiotherapy administered by hypofractionated schedule is an effective and safe option in the treatment of locally confined prostate cancer. With an appropriate use of hormonal therapy, satisfactory biochemical control can be achieved even in high-risk patients. Trials with greater hypofractions have started at NIRS with the aim of establishing even more sophisticated methods of C-ion RT.

References

[1] Nikoghosyan A, Schulz-Ertner D, Didinger B, et al: Evaluation of therapeutic potential of heavy ion therapy for patients with locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 58(1): 89-97, 2004

[2] Perez CA, Michalski J: Outcome of external-beam radiation therapy for localized carcinoma of the prostate (stages T1b, T2, and T3). In: Greco C, Zelefsky MJ, editors. Radiotherapy of prostate cancer. Amsterdam: Harwood Academic Publishers; p.155-184, 2000

[3] Hanks GE, Hanlon AL, Pinover WH, et al: Dose escalation for prostate cancer patients based on dose comparison and dose response studies. Int J Radiat Oncol Biol Phys 2000; 46: 823-832.
[4] Zelefsky MJ, Fuks Z, Hunt M, et al: High-dose intensity modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002; 53: 1111-1116.
[5] Laramore GE, Krall JM, Thomas FJ, et al: Fast neutron radiotherapy for locally advanced prostate cancer: final report of a Radiation Therapy Oncology Group randomized clinical trial. Am J Clin Oncol 1993; 16: 164-167.
[6] Haraf DJ, Rubin SJ, Sweeney P, et al: Photon neutron mixed-beam radiotherapy of locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 1995; 33: 3-14.
[7] Tsujii H, Morita S, Miyamoto T, et al: Preliminary results of phase I/II carbon-ion therapy at the National Institute of Radiological Sciences. J Brachytherapy Int 1997; 13: 1-8.
[8] Akakura K, Tsujii H, Morita S, et al: Phase I/II clinical trials of carbon ion therapy for prostate cancer. Prostate 2004; 58: 252-258.
[9] Tsuji H, Yanagi T, Ishikawa H, et al: Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 63(4): 1153-1160.
[10] Ishikawa H, Tsuji H, Kamada T, et al; A phase II trial using carbon ion radiotherapy (C-ion RT) for prostate cancer. JCO 23(16) part 1 Supple. 2005; 410S-410S.
[11] Ishikawa H, Tsuji H, Kamada T, et al: Carbon Ion Radiation Therapy for Prostate Cancer: Results of a Prospective Phase II Study. Radiother Oncol in press.
[12] International Union Against Cancer (UICC). TNM Classification of Malignant Tumours, 5th ed. New York: Wiley-Liss, Inc. 1997; p 170-173.
[13] Bolla M, Gonzalez D, Warde P, et al: Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997; 337: 295-300.
[14] Roach MIII, Lu J, Pilepich MV, et al: Predicting long-term survival, and the need for hormonal therapy: a meta-analysis of RTOG prostate cancer trials. Int J Radiat Oncol Biol Phys 2000; 47: 617-627.

Carbon Ion Radiotherapy in Bone and Soft Tissue Sarcomas

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Abstract

The Heavy Ion Medical Accelerator in Chiba (HIMAC) is the world's first heavy ion accelerator complex dedicated to medical use in a hospital environment. Heavy ions have superior depth-dose distribution and greater cell-killing capability. In June 1996, clinical research for the treatment of bone and soft tissue sarcomas was begun using carbon ions generated by the HIMAC. As of August 2009, a total of 471 patients with bone and soft tissue sarcoma were enrolled into the clinical trials. Most of the patients had locally advanced and/or medically inoperable sarcomas. The clinical trial revealed that carbon ion radiotherapy provided definite local control and offered a survival advantage without unacceptable morbidity in bone and soft tissue sarcomas that were hard to cure with other modalities.

1. Introduction

Tumors arising from bones, muscles, and vessels are referred to as bone and soft tissue sarcomas. While the incidence of these tumors is extremely low, they are capable of occurring ubiquitously throughout the body. For this reason, they are occasionally detected too late or their accurate diagnosis presents difficulty and incomplete treatment is administered on the false recognition of their being benign.

While tumor resection is the most common treatment modality for such bone and soft tissue sarcomas, major progress has been made in their management, thanks to the development of combined therapy modalities in recent years, in the wake of surgical advancements. These methods combine chemotherapy and radiotherapy with new imaging diagnostics such as MR, CT, and PET. Among these tumors, osteosarcoma originating in the limbs accounts for the majority of malignant bone tumors, and limb-sparing surgery not requiring arm or leg amputation has become possible through a combination of surgical resection with chemotherapy. The therapeutic results have also recorded a dramatic improvement in recent years: Whereas the five-year survival rate was only 10-20% in the 1970s, the latest data are up to as high as 50 - 80%. Similarly, soft tissue sarcomas developing in muscle or other soft tissues have meanwhile come to be treated by combined chemo-radiotherapy modalities and functional preservation operations achieving a five-year survival rate in excess of 70%. In the case of tumors that have developed in or near the spinal cord or in the pelvis, as well as advanced limb tumors and postoperative recurrent tumors, however, chemotherapy may often not be very effective and curative surgery may be difficult to perform. Moreover, most bone and soft tissue sarcomas are known to be resistant to conventional radiation. Thus, despite the significant progress seen in the treatment of bone and soft tissue sarcomas in recent years, patients judged intractable to surgery still face the harsh reality of being less likely to find an effective treatment option. In this regard, carbon ion radiation with its superior dose conformity and its potent biological effect holds out much promise for also achieving outstanding results with radio-resistant bone and soft tissue sarcomas. This

article presents our experiences with carbon ion radiotherapy using the Heavy Ion Medical Accelerator in Chiba (HIMAC) at NIRS.

2. Patients and Methods

A dose escalation trial (phase I/II trial) using carbon ion beams was carried out on 64 lesions of 57 bone or soft tissue sarcoma patients during the period from June 1996 until February 2000 [1]. A fixed-dose phase II trial was then initiated in April 2000, and records as of February 2009 show that 406 lesions of 387 patients have been treated. Both of these trials included bone or soft tissue sarcoma patients for whom surgical resection was contra-indicated. The main eligibility criteria are listed in Table 1. While the phase II trial included patients with radiation-associated sarcoma, it did exclude patients with intravascular tumor embolus. Four hundred and forty-four patients (470 lesions) in these 2 trials have been followed for 6 months or longer after carbon ion treatment as of August 2009. Their clinical characteristics are summarized in Table 2. There were 260 males and 184 females, and their age ranged from 11 to 87 years, with a median of 52 years. Tumor locations were as follows: 96 lesions in the spine or paraspinal region; 341 in the pelvis, and 33 in the extremities and other sites. The tumors were categorized as 344 primary bone and 100 primary soft tissue sarcomas. Histological classification showed that chordoma was the most frequent tumor, accounting for 145 patients, followed by osteosarcoma in 75 patients, chondrosarcoma in 66 patients, MFH (including 18 bone primaries) in 36 patients and Ewing/PNET in 30 patients (including 5 soft tissue primaries). For pathological confirmation, central pathological review of surgical or biopsy specimen was carried out. All patients enrolled in the trials gave their written informed consent.

Table 1. Eligibility

• Histologically confirmed bone or soft tissue sarcomas
• Unresectable or declines surgery
• Gross measurable lesion
• Lesion size <15cm in maximum diameter
• KPS 60~100%
• No prior radiotherapy to the lesion
• Signs informed consent statement

Abbreviations: KPS, Karnofsky performance status

Table 2. Patient characteristics

Characteristic		No. (N =444)
Age, years		
Median (range)		52 (11~87)
Sex		
Female/ Male		184/260
Tumor sites (470 lesions)		
Pelvis		341
Spine/para-spine		96
Extremities etc		33
Histology		
	Bone	344
	Chordoma	145
	Osteosarcoma	75
	Chondrosarcoma	66
	PNET	25
	MFH	18
	Others	15
	Soft tissue	100
	MFH	18
	Synovial sarcoma	10
	Liposarcoma	9
	PNET	5
	Leiomyosarcoma	6
	Rhabdomyosarcoma	5
	Others	30
Clinical target volume, cm^3		
Mean (range)		502 (16~2900)

Abbreviations: PNET, primitive neuroectodermal tumor; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor

The features of the Heavy Ion Medical Accelerator in Chiba (HIMAC) and the carbon ion beam have been previously described. In brief, the accelerated carbon ion beam energies were 290, 350, and 400 MeV. The range of the beams was a depth of 15− 25 cm in water. An appropriately sized ridge filter corresponding to the tumor size was selected to form the spread-out Bragg peak (SOBP). A compensation bolus was fabricated for each patient to make the distal configuration of the SOBP similar to the shape of the target volume. A multi-leaf collimator defined the margins of the target volume. Patients were placed in customized cradles and immobilized with a low-temperature thermoplastic sheet. A set of 5-mm-thick CT images was taken for the treatment planning. Three-dimensional treatment planning was performed with HIPLAN software (National Institute of Radiologic Sciences, Chiba, Japan) for the planning of carbon ion therapy. A margin of 5 mm was usually added to the clinical target volume to create the planning target volume. When the tumor was located close to critical organs such as the spinal cord, skin or bowel, the margin was reduced accordingly. The clinical target volume was covered by at least 90% of the prescribed dose. Dose was calculated for the target volume and any nearby critical structures and expressed in Gray-Equivalent (GyE = carbon physical dose (Gy) x Relative Biological Effectiveness {RBE}). Carbon ion radiotherapy was given once daily, 4 days a week (Tuesday to Friday), for a fixed 16 fractions in 4 weeks. Patients were treated with two to eight irregularly shaped ports (median, 3 ports).

One port was used in each session. At every treatment session, the patient's position was verified with a computer-aided on-line positioning system. The patient was positioned on the 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 the isocenter position was less than 2 mm. For all of these patients, a total dose ranging from 52.8 GyE to 73.6 GyE was administered by a fractionation regimen of 16 fractions over four weeks (with single radiation doses of 3.3 - 4.6 GyE).

3. Results

A dose escalation trial (phase I/II trial) with a total dose ranging from 52.8 GyE to 73.6 GyE administered in 16 fractions over four weeks (single radiation doses of 3.3 - 4.6 GyE) was carried out on 64 lesions of 57 bone and soft tissue sarcoma patients between June 1996 and February 2000. As 7 of the 17 patients treated with 73.6 GyE were found to have grade 3 RTOG acute reactions (skin), dose escalation was halted at this dose level. No other grade 3 or worse acute reactions were detected. These findings made it clear that with a fractionation regimen of 16 fractions over four weeks, a total dose of 70.4 GyE was the maximum applicable dose in cases in which skin presented a problem, and a total dose of 73.6 GyE was possible in other cases. The overall local control rate was 89% at 1 year, 63% at 3 years, and 63% at 5 years. A significant difference was found between the local control rates achieved with a total dose of 57.6 GyE or less and those with 64.0 GyE or more. The median survival period was 31 months (2-96 months), and the 1-, 3- and 5-year survival rates were 82%, 47%, and 37%, respectively. A fixed-dose phase II trial was then initiated in April 2000, and as of August 2009, 414 patients have been enrolled for treatment. The number of lesions and patients analyzed six months or longer after therapy stands at 406 lesions of 387 patients, with 10 of these lesions having been treated with a dose of 73.6 GyE (4.6 GyE per fraction), 27 with 64 GyE (4.0 GyE per fraction) and 43 with 67.2 GyE (4.2 GyE per fraction). The remaining 326 lesions were treated with a dose of 70.4 GyE (4.4 GyE per fraction). As of the present, the 2- and 5-year local control rates are 88% and 79%, and similarly, the overall survival rates are 78% and 61%, respectively (Figure 1).

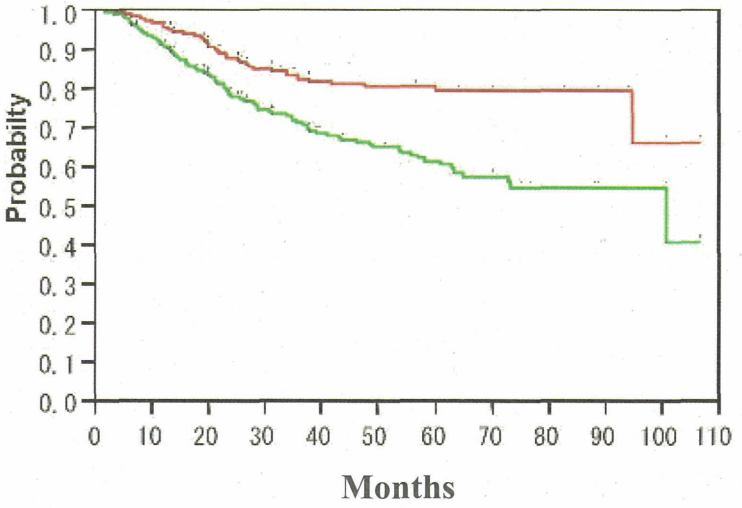


Figure 1. Acutuarial local control and overall survival in the 387 phase II study patients with bone or soft tissue sarcomas. Local control rate at 5 years was 79%, and overall survival rate at 5 years was 61%.

Radiation morbidities are summarized in Table 3. Grade 3 or worse toxic reactions included 2 patients with acute skin toxicities (grade 3) and 7 patients with late skin toxicities (grade 3: 6 patients; grade 4: 1 patient). These late skin reactions suggest that the following may be risk factors in addition to the total dose: 1) subcutaneous tumor invasion, 2) tumor volume, 3) sacrum, 4) previous surgery, 5) additional chemotherapy, and 6) irradiation from two portals. It was possible, however, to prevent these reactions by aiming for a standard dose of 70.4 GyE and by modifying the irradiation method that may include irradiation from three portals, in order to reduce the dose delivered to the skin.

The entire evaluable population for both the above clinical trials amounted to 470 lesions of 444 patients, and their aggregate 5-year local control rate presently stands at 72% and their 5-year overall survival rate at 57% (Figure 2). The 45 chordoma patients (excluding patients with the base of the skull primaries) of this total have a 5-year local control rate of 85% and a 5-year overall survival rate of 85% (Figure 3) (A report on the 30 sacral chordoma patients who were observed for a period of two years or longer was published in the Clinical Cancer Research [2]).The 5-year local control rate and 5-year overall survival rate for the 75 patients with osteosarcoma were 64% and 29% (Figure 4) and for the 66 chondrosarcoma patients, 59% and 62%, respectively. (Figure 5)

Table 3. Radiation morbidities in the phase II study

		Grade					
	No.	0	1	2	3	4	5
Skin							
Early	405	1	364	36	4	0	0
Late	397	4	367	18	6	1	0
GI tract							
Early	359	354	5	0	0	0	0
Late	353	352	1	0	0	0	0
Lung							
Early	32	32	0	0	0	0	0
Late	32	30	2	0	0	0	0
Edema	17	13	3	1	0	0	0
Spinal cord	39	38	0	1	0	0	0

Early: RTOG, Late: RTOG/EORTC, SOMA/LENT

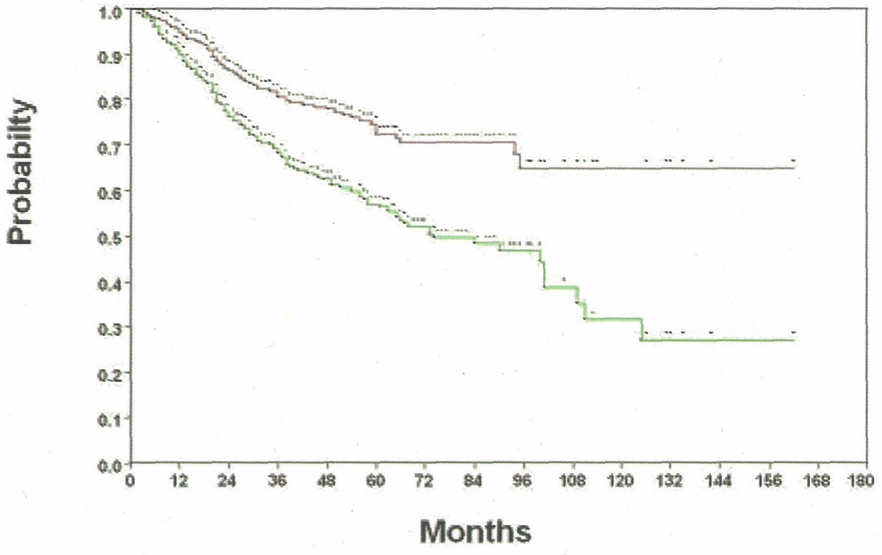


Figure 2. Actuarial local control and overall survival in the 444 patients (470 lesions) with bone or soft tissue sarcomas. Local control rate at 5 years was 72%, and overall survival rate at 5 years was 57%.

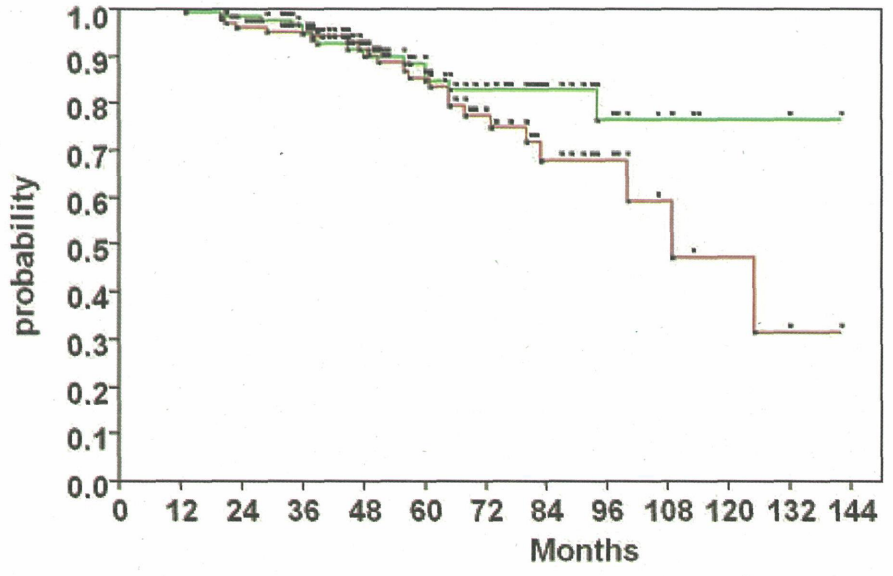


Figure 3. Actuarial local control and overall survival in the 145 patients with chordoma. Local control rate at 5-years was 85%, and overall survival rate at 5-years was 85%.

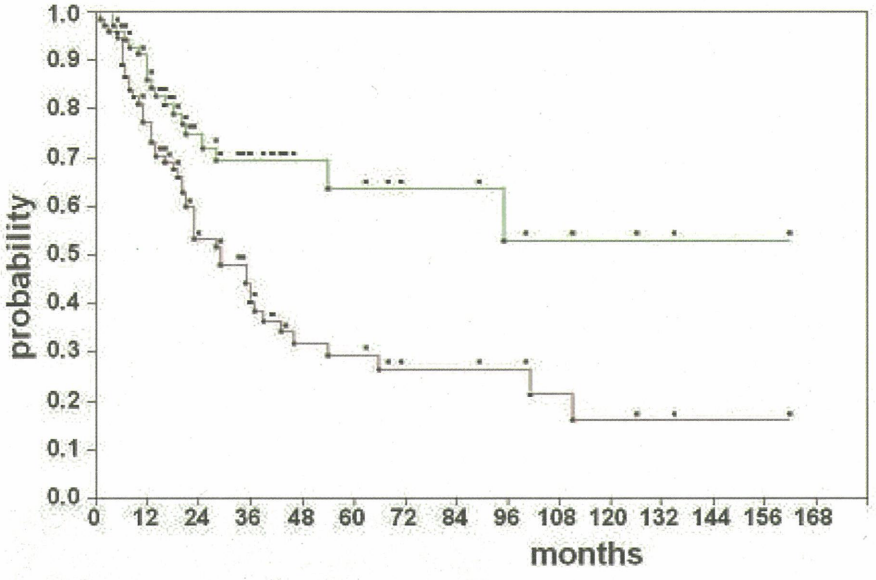


Figure 4. Actuarial local control and overall survival in the 75 patients with osteosarcoma. Local control rate at 5 years was 64%, and overall survival rate at 5 years was 29%.

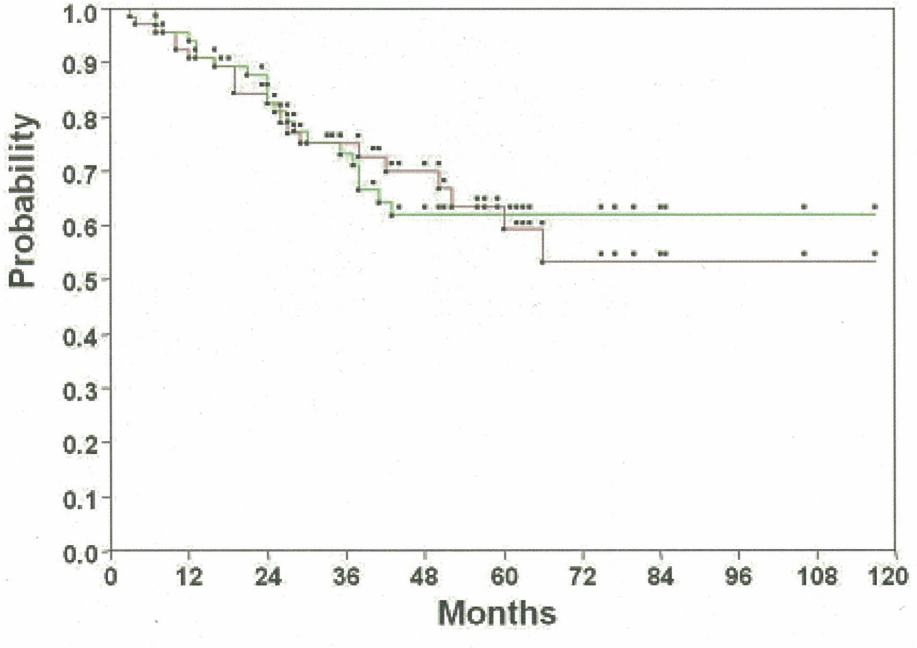


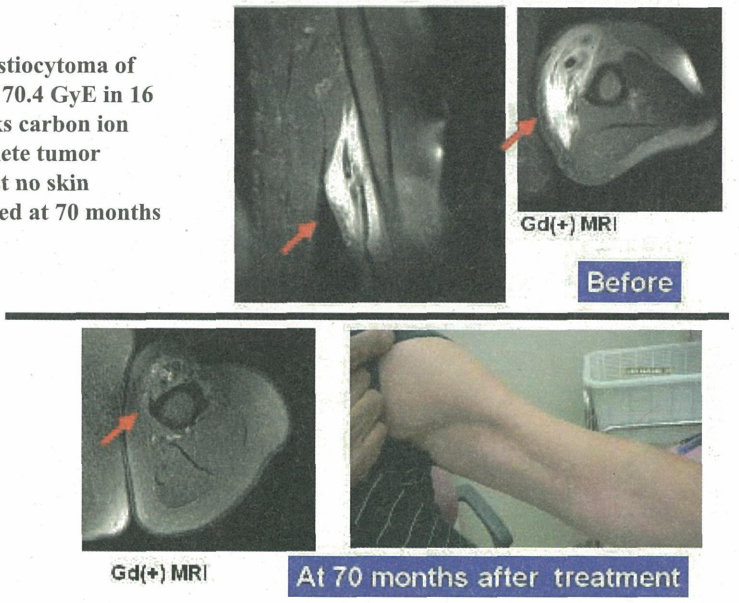
Figure 5. Actuarial local control and overall survival in the 66 patients with chondrosarcoma. Local control rate at 5 years was 59%, and overall survival rate at 5 years was 62%.

4. Discussion

In this study, carbon ion radiotherapy was well tolerated and demonstrated substantial activity against sarcomas[1][2][3]. These results were obtained in patients with advanced and/or chemo-resistant gross lesions not suited for surgical resection and located mainly in the trunk. Irradiation with a total dose ranging from 64 to 73.4 GyE in 16 fractions over four weeks resulted in a local control rate of almost 80% for bone and soft tissue

sarcomas disqualified from surgery. Although treatment results after carbon ion radiotherapy have so far been quite satisfactory, it is imperative to continue with long-term follow-up observation and carry out further analyses to assess local control, toxicities, survival rate and QOL as a function of such criteria as histological type, location, tumor size, irradiation field and dose to achieve a safe and effective therapy regimen. For small lesions, in particular, the possibilities of a shorter irradiation regimen should be explored. Systematic analyses will be essential to determine the optimum dose and irradiation field setting in accordance with the patient's histological type and tumor location and to shed light on the problems involved. Research will also be needed to clarify the role of heavy particle radiotherapy in the context of combined therapy modalities for bone and soft tissue sarcomas. Not only for patients disqualified from surgery but also for elderly patients and patients with major functional loss consequent to surgical resection, carbon ion radiotherapy is seen as a valid alternative to surgery. While previous experience with carbon ion radiotherapy to the extremities has so far been rather limited, the combination of carbon ion radiation and surgery could offer a promising potential for patients intractable to limb-sparing surgery as a modality for widening the scope of limb-retaining therapy. (Figure 6)

Figure 6.
Malignant fibrous histiocytoma of the left arm received 70.4 GyE in 16 fractions over 4 weeks carbon ion radiotherapy. Complete tumor regression and almost no skin reaction were observed at 70 months after treatment.



5. 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 quite acceptable, although the long-term safety of this approach for patients with sarcomas will need to be monitored.

References

[1] Kamada T, Tsujii H, Tsuji H, et al. Efficacy and Safety of Carbon Ion Radiotherapy in Bone and Soft Tissue Sarcomas. Journal of Clinical Oncology. 2002;20:4466-4471.

[2] Imai R, Kamada T, Tsuji H, et al. Carbon Ion Radiotherapy for Unresectable Sacral Chordomas. Clinical Cancer Research. 2004;10:5741-5746.

[3] Serizawa I, Kagei K, Kamada T, et al. Carbon ion radiotherapy for unresectable retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys. 2009;75(4):1105-10.

Carbon Ion Radiotherapy for Skull Base and Head-and-Neck Tumors

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1. Skull Base and Paracervical Tumors

Abstract

To estimate the toxicity and efficacy of the clinical trials for patients with skull base and paracervical tumors treated with carbon ion radiotherapy.

A phase I/II dose escalation study for skull base and paracervical tumor was initiated in April 1997. The phase I/II dose escalation trial was performed up to the fourth-stage dose level. From 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 four weeks.

At the time of analysis, there was no evidence of any serious acute or late reactions in skull base and paracervical tumors. For skull base and paracervical tumor, the carbon ion dose in excess of 57.6 GyE improves local control.

Introduction

The limiting factor for photon radiotherapy conventionally applied to the skull base and paracervical tumors is the adjacent normal tissue, seeing that photon radiotherapy has poor local control. On the other hand, proton radiotherapy with its superior physical-spatial distribution has provided a major improvement in local control in view of 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 offer a worse prognosis than chondrosarcoma patients, 2) among chordoma patients, the prognosis for paracervical chordoma patients is worse than for skull base chordoma, it is worse for non-chondroid patients than for chondroid ones, and it is worse for females than for males, and 3) for meningeal tumors, the prognosis for the atypical or malignant types is worse than for the benign type, and the prognosis for the age group of 60 and above is poorer than for those under 60. Therefore, the high RBE of carbon ion radiotherapy has a promising potential for these intractable skull base and paracervical tumors.

Patients and Methods

A phase I/II clinical trial (Protocol 9601) was initiated in April 1997. Chordoma, meningioma, chondrosaracoma and other tumors originating 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 partake in the carbon ion radiotherapy. The eligibility criteria for enrollment in this clinical trail were the presence of histologically proven tumor, patient age ranging from 15 to 80 years, KPS of 60% or more, neurological function of grade I or II, absence of anti-cancer chemotherapy within the previous four weeks, survival expectancy of six months or more, and no distant metastasis to other parts. In the meantime, the carbon ion dose was escalated in successive stages: 48.0 GyE (4 patients), 52.8 GyE (6 patients), 57.6 GyE (10 patients) and 60.8 GyE (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. Thirty-three patients had been enrolled into this trial up to August 2009.

Acute toxicity was assessed based on the Radiation Therapy Oncology Group (RTOG) score, 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.

The 62 patients included in the analysis between May 1995 and August 2009 consisted of 30 males and 32 females. One female patient with chondrosarcoma had to be excluded because she was treated with surgery for metastasis and her diagnosis was changed to malignant melanoma. She was treated with 57.6 GyE. The age range of the 61 patients was from 16 to 78, with a median of 51 years. Histologically, 37 patients had chordoma, 10 chondrosarcoma, 7 malignant meningioma, 6 olfactory neuroblastoma and 1 giant cell carcinoma.

Results

Acute reactions were of a minor nature, as one patient of the 48 GyE group showed a grade 3 skin reaction, one patients of the 57.6 GyE and 2 patients of the 60.8 GyE groups showed a grade 3 mucosal reaction. A late grade 2 brain reaction was detected in 2 patients, but no other adverse reactions were discovered. At the time of analysis, there was no evidence of any serious acute or late reactions.

The tumor effect remains mostly as stable disease (SD) within six months after carbon ion radiotherapy, and there were in most cases no changes in tumor size during the follow-up periods. Local control was defined as showing no evidence of tumor regrowth by MRI, CT, physical examination, or biopsy. The five-year local control (LC) rates according to histological types were 81% for the 37 chordomas, 100% for the 10 chondrosarcomas, 80% for the 7 malignant meningiomas, and 100% for the 6 olfactory neuroblastomas. The five-year overall survival (OS) rate was 88% for chordomas, 64% for chondrosarcomas, 83% for malignant meningiomas, and 100% for olfactory neuroblastomas. Two of the seven malignant meningioma patients died because of distant metastasis 23 months, and local recurrence 85 months, respectively, after carbon ion radiotherapy. This local recurrence patient had had a postoperative recurrence and received low-dose carbon ion radiotherapy of 52.8 GyE.

The 37 chordoma patients were divided into two groups, a low-dose group (n=10) irradiated with doses ranging from 48 to 57.8 GyE and a high-dose group (n=27) irradiated with 60.8 GyE. The five-year LC rates were 60% for the low-dose group and 94% for the high-dose group (Fig. 1). One patient of the high-dose group developed marginal failure 29 months later. The five-year OS rates were 90% for the low-dose group and 89% for the high-dose group. Two patients from the high-dose group died due to hepatic failure and marginal failure.

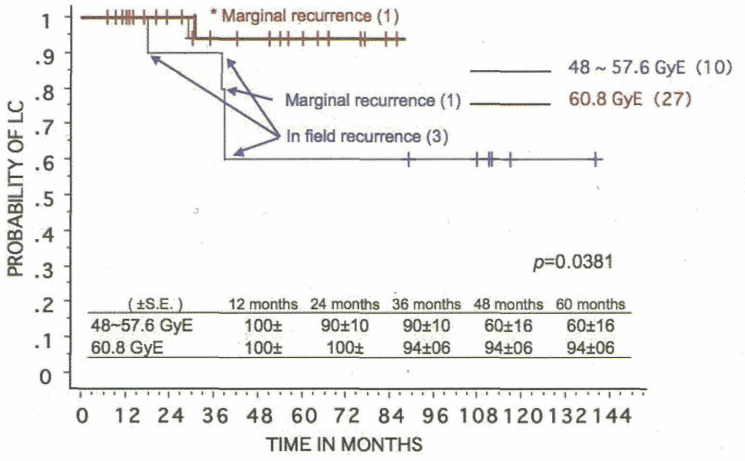

Figure 1. Local Control of 37 Chordomas according to Carbon Ion Dose

Discussion

The carbon ion dose in excess of 57.6 GyE improves local control. Additionally, we did not observe severe toxicity to critical organs such as the brainstem, spinal cord and optic nerves. From April 2004, 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 potentiality can cause severe damage to the tumor while lessening the effects on normal tissue. When the tumor was located close to critical organs, delineation of the CTV was done with efforts to spare them. In particular, when both optic nerves were involved in the high-dose area, treatment planning was performed to spare the contralateral optic nerve and chiasm according to our previous dose criteria [1]. For tumors close to the brainstem and spinal cord, we recommend surgical resection to create a space between the tumor and brainstem or spinal cord before carbon ion radiotherapy. This allows the prevention of severe toxicity to the brainstem and spinal cord. Tumors such as chordoma can thus only be judged on the results of long-term prognosis. Consequently, it will take more time to reach a definitive conclusion. It is clear that carbon ion radiotherapy compared with photon or other charged particle radiotherapy will deliver a high local control rates with low toxicity to the surrounding normal tissues (Table 1)[2-14].

Table1. Clinical characteristics of reported cases of chordoma in the skull base

	Authors	N	Median total dose	Median f/u (y)	Local control rate (%) 3-y	5-y	10-y
Photon	Catton et al. [4]	24	50.0	5.2		23	15
	Romero et al. [5]	18	50.1	3.1		17	
	Forsyth et al. [6]	39	50.0	8.3		39	31
	Magrini et al. [7]	12	58.0	6.0		25	25
Proton	Munzenrider et al. (MGH) [8]	169	66-83	3.4		73	54
(+/- photon)	Noel et al. (CPO) [9]	100	67.0	2.6	86 (2-y)	54 (4-y)	
	Igaki et al. (Tsukuba) [10]	13	72.0	5.8	67	46	
	Ares et al. (PSI) [11]	42	73.5	3.2 (Mean)		81	
Helium	Castro et al. (LB) [12]	53	65.0	4.3		63	
Carbon	Shults-Ertner et al. (GSI) [13]	96	60.0	2.6 (Mean)	81	70	
	NIRS [14]	36	48-60.8	4.6		81	81
	NIRS	27	60.8	3.8		94 (7-y)	

Conclusion

In this phase I/II clinical study for skull base and paracervical tumors, dose escalation trials were performed up to the fourth-stage dose level. Because dose escalation is implemented after checking the reactions of the important adjacent organs – the brain and spinal chord – the scheduled enrollment period was exceeded and therapy was commenced under the Highly Advanced Medical Technology scheme for these patients in April 2004 with a dose fractionation regimen of 60.8 GyE in 16 fractions over 4 weeks. The carbon ion dose in excess of 57.6 GyE improves local control.

2. Head-and-Neck Tumors

Abstract

To evaluate the efficacy of carbon ion radiotherapy for malignant head-and-neck tumors.

Between April 1997 and August 2009, 363 cases with locally advanced, histologically proven, and new 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 37% 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.

2-1. 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 [15], 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. 2).

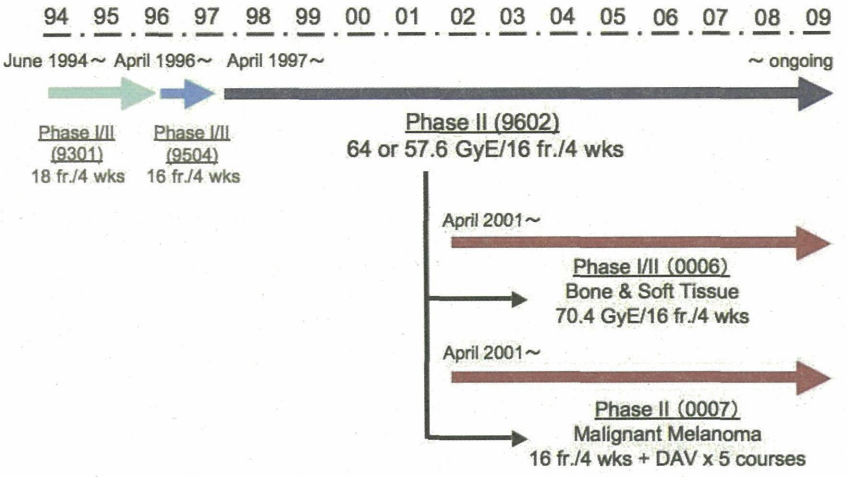

Figure 2. Carbon Ion Radiotherapy for Malignant Head-and-Neck Tumors

Patients and Methods

The eligibility criteria for enrollment in this clinical trial 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 a interval of at least four weeks from completion of the last chemotherapy.

The clinical trial commenced in April 1997, and by August 2009 a total of 365 patients with 368 lesions was registered (three patients had secondary lesions after the initial treatment). Five of the 365 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 363 lesions of 360 patients treated until August 2009 are recorded as follows: Patient age range was from 16 to 80, with a median of 58 years, with 180 males and 183 females. Histologically, the tumors were classified as follows: 129 with adenoid cystic carcinoma, 102 with malignant melanoma, 42 with adenocarcinoma, 20 with squamous cell carcinoma, 13 with papillary adenocarcinoma, 12 with mucoepidermoid carcinoma, 6 with osteosarcoma, 6 with acinic cell carcinoma, 5 with undifferentiated carcinoma and 28 with other histological types. There were five cases of T1, 29 of T2, 54 of T3, 155 of T4, 83 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 363 lesions were irradiated with a dose of 57.6GyE in 243 cases and with 64.0GyE in 120 cases.

Results

Acute reactions were of a minor nature, as 15 patients (4%) showed a grade 3 skin reaction, 56 patients (16%) showed a grade 3 mucosal reaction. Late toxic reactions comprised of a grade 2 skin reaction in 8 patients (2%) and mucosal reactions in 12 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 47 patients, PR for 164 patients, NC for 144 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 42 adenocarcinomas, 76% for the 129 adenoid cystic carcinomas, 76% for the 102 malignant melanomas, 75% for the 20 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, 37% 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 [16-19] (Table 2). In the present study, the five-year LC rate was 76%, in spite of including 69 cases (53%) of T4 and 35 cases (27%) that had recurrent tumors after surgery and/or chemotherapy.

Table2. Clinical characteristics of reported cases of adenoid cystic carcinoma

Institutions	N		5-year local control rate (%)	5-year survival rate (%)
Florida [16]	101	Radiotherapy alone	56	57
		Radiotherapy + Surgery	91	77
MGH [17]	23	Proton +/- Surgery	93	77
Washington [18]	151	Neutron	57	77
Heidelberg [19]	29	Neutron +/- Surgery	75	59
NIRS	129	Carbon	76	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 Sarocomas 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.

2-2.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 worth 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 [20], 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 35 patients included in the analysis between April 2001 and August 2009 consisted of 18 males and 17 females. Two of the 35 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 33 patients was from 17 to 78, with a median of 46 years. They consisted of 11 patients with osteosarcoma, 5 with MFH, 2 with chondrosarcoma, 2 with hemangiopericytoma, 2 with myxofibrosarcoma, 2 with leimyosarcoma, 2 with small round cell sarcoma, and 7 with other histological types.

Results

In preliminary analysis of the 33 patients who had follow-up period for more than six months, almost of all patients presented less than grade 2 acute reactions; however, only one patient 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 4 patients, PR for 6 patients, SD for 23 patients, and PD for no patients. The response rate was 30%. The five-year LC and OS rates were 79% and 54%, respectively (Fig. 3).

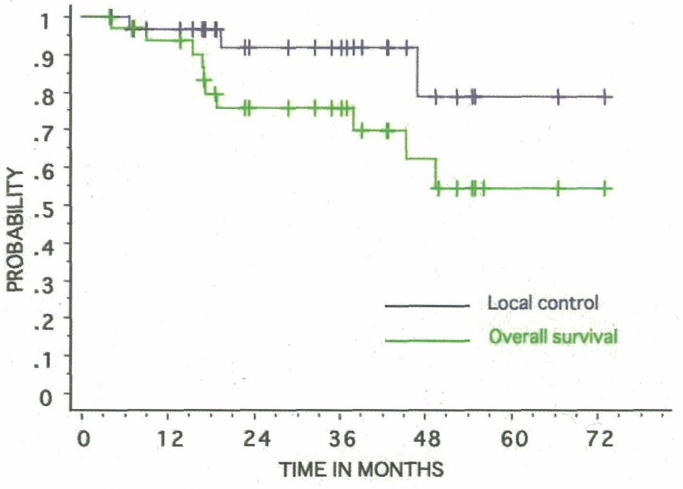

Figure 3. Local Control and Overall Survival of Bone and Soft Tissue Sarcomas

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 [21]. 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% [22]. 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 [23-25].

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 79%. This result showed improved tendency compared with surgery with or without radiotherapy.

2-3.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 92 patients included in the analysis between April 2001 and August 2009 consisted of 40 males and 52 females. Their age ranged from 26 to 74 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 74 nasal cavity and paranasal sinus, 11 oral cavity, 4 pharynx and 3 orbit.

Results

The acute reactions of 92 patients who have a follow-up time more than 6 months were consisted of one patient with a grade 3 skin reaction and 17 patients (18%) 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 20 patients, PR for 42 patients, SD for 31 patients, and PD for no patients. The effective rate was 67%. The five-year LC and OS rates of all patients were 79% and 57%. In 85 concomitant patients, the five-year LC and OS rates were 81% and 62%, respectively.

Discussion

The reported local failure of systemic therapy including surgery, radiotherapy and chemotherapy is very high (45-54%) [26, 27]. 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 [28-34] reported the five-year survival rates of 17-35% (Table 3), which is attributed mainly to distant metastasis. The five-year OS rate of carbon ion radiotherapy showed 37% in 9602 and 57% in 0007 protocol. There will be some tendency of improving result in concomitant and adjuvant chemotherapy (Protocol 0007) (Fig. 4).

Table3. Clinical characteristics of reported cases of mucosal malignant melanoma

	Authors	N	5-year OS (%)
Radiotherapy	Gilligan [28]	28	18
(+/- Surgery)	Shibuya [29]	28	25
Surgery	Chang [30]	163	32
(+/- RT, +/- Chemo)	Shah [31]	74	22
	Patel [32]	59	35
	Lund [33]	58	28
	Chaudhry [34]	41	17
Carbon ion alone	NIRS	102	37
Carbon ion + Chemo	NIRS	85	62

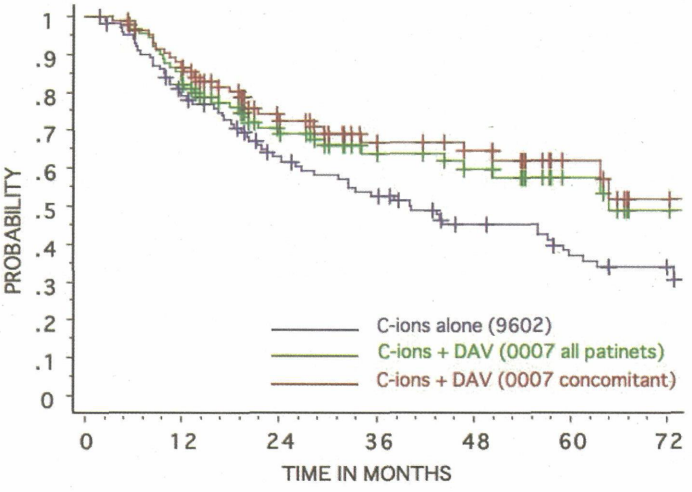

Figure 4. Overall Survival of Mucosal Malignant Melanomas

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.

References

[1] Hasegawa A, Mizoe J, Mizota A, Tsujii H. Outcomes of visual acuity in carbon ion radiotherapy: analysis of dose–volume histograms and prognostic factors. *Int J Radiat Oncol Biol Phys*, 2006; 64 (2): 396-401.

[2] Tsujii H, Mizoe J, Kamada T, *et al*. Overview of clinical experiences on carbon ion radiotherapy at NIRS. *Radiother Oncol* 2004;73:41–49.

[3] Tsujii H, Mizoe J, Kamada T, *et al*. Clinical results of carbon ion radiotherapy at NIRS. *Radiat Res* 2007;48:A1–13.

[4] Catton C, O'Sullivan B, Bell R, *et al*: Chordoma: Long-term follow-up after radical photon irradiation. *Radiother Oncol.* 1996; 41: 67-72.

[5] Romero J, Cardenes H, la Torre A, *et al*: Chordoma: Results of radiation therapy in eighteen patients. *Radiother Oncol.* 1993; 29: 27-32.

[6] Forsyth PA, Cascino TL, Shaw EG, *et al*: Intracranial chordomas: A clinicopathological and prognostic study of 51 cases. *J Neurosurg.* 1993; 78: 741-747.

[7] Magrini SM, Papi MG, Marletta F, *et al*: Chordoma- natural history, treatment and prognosis. The Florence Radiotherapy Department experience (1956-1990) and a critical review of the literature. *Acta Oncol.* 1992; 31: 847-851.

[8] Munzenrider JE, Liebsch NJ: Proton therapy for tumors of the skull base. *Strahlenther Onkol.* 1999; 175: 57-63.

[9] Noël G, Habrand JL, Jauffret E, *et al*: Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. *Strahlenther Onkol.* 2003; 179(4): 241-248.

[10] Igaki H, Tokuuye K, Okumura T, *et al*: Clinical results of proton beam therapy for skull base chordoma. *Int J Radiat Oncol Biol Phys.* 2004; 60: 1120-1126.

[11] Ares C, Hug EB, Lomax AJ, *et al*: Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys.* 2009; 75(4): 1111-1118.

[12] Castro JR, Linstadt DE, Bahary JP, *et al*: Experience in charged particle irradiation of tumors of the skull base: 1977-1992. *Int J Radiat Oncol Biol Phys.* 1994; 29: 647-655.

[13] Schulz-Ertner D, Karger CP, Feuerhake A, *et al*: Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. *Int J Radiat Oncol Biol Phys.* 2007; 68(2): 449-457.

[14] Mizoe J, Hasegawa A, Takagi R, , *et al*: Carbon ion radiotherapy for skull base chordoma. *Skull Base,* 2009; 19 (3): 219-224.

[15] Mizoe J, Tsujii H, Kamada T, *et al*: Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2004; 60: 358-364.

[16] Mendenhall WM, Morris CG, Amdur RJ, *et al*: Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. *Head Neck*. 2004; 26(2): 154-162.

[17] Pommier P, Liebsch NJ, Deschler DG, *et al*: Proton beam radiation therapy for skull base adenoid cystic carcinoma. *Arch Otolaryngol Head Neck Surg*. 2006; 132(11): 1242-1249.

[18] Douglas JG, Laramore GE, Austin-Seymour M, *et al*: Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. *Int J Radiat Oncol Biol Phys.* 2000; 46(3): 551-557.

[19] Huber PE, Debus J, Latz D, *et al*: Radiotherapy for advanced adenoid cystic carcinoma: neutrons, photons or mixed beam? *Radiother Oncol.* 2001; 59(2): 161-167.

[20] Kamada T, Tsujii H, Tsuji H, *et al*: Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. *J Clin Oncol.* 2002; 20: 4466-71.

[21] Willers H, Hug EB, Spiro IJ, *et al*: Adult soft tissue sarcomas of the head and neck treated by radiation and surgery or radiation alone: patterns of failure and prognostic factors. *Int J Radiat Oncol Biol Phys.* 1995; 33: 585-593.

[22] Mendenhall WM, Mendenhall CM, Werning JW, *et al*: Adult head and neck soft tissue sarcomas. *Head Neck.* 2005: 27: 916-922.

[23] Le QT, Fu KK, Kroll S, *et al*: Prognostic factors in adult soft-tissue sarcomas of the head and neck. *Int J Radiat Oncol Biol Phys.* 1997; 37: 975-984.

[24] Barker JL Jr, Paulino AC, Feeney S, *et al*: Locoregional treatment for adult soft tissue sarcomas of the head and neck: an institutional review. *Cancer J.* 2003; 9: 49-57.

[25] Chen SA, Morris CG, Amdur RJ, *et al*: Adult head and neck soft tissue sarcomas. *Am J Clin Oncol.* 2005; 28: 259-263.

[26] Mendenhall WM, Amdur RJ, Hinerman RW, *et al*: Head and neck mucosal melanoma. *Am J Clin Oncol.* 2005; 28: 626-630.

[27] Lengyel E, Gilde K, Remenár E, *et al*: Malignant Mucosal Melanoma of the Head and Neck -a Review-. *Pathology Oncology Research.* 2003; 9: 7-12.

[28] Gilligan D, Slevin NJ: Radical radiotherapy for 28 cases of mucosal melanoma in the nasal cavity and sinuses. *Br J Radiol.* 1991; 64:1147-1150.

[29] Shibuya H, Takeda M, Matsumoto S, *et al:* The efficacy of radiation therapy for malignant melanoma in the mucosa of the upper jaw: an analytic study. *Int J Radiat Oncol Biol Phys.* 1992; 25: 35-39.

[30] Chang AE, Karnell LH, Menck HR: The National Cancer Data Base Report on cutaneous and noncutaneous melanoma. *Cancer.* 1998; 83: 1664-1678.

[31] Shah JP, Huvos AG, Strog EW: Mucosal melanomas of the head and neck. *Am J Surg.* 1977; 134: 531-535.

[32] Patel SG, Prasad ML, Escrig M, *et al*: Primary mucosal malignant melanoma of the head and neck. *Head Neck.* 2002; 24: 247-257.

[33] Lund VJ, Howard DJ, Harding L, *et al*: Management options and survival in malignant melanoma of the sinonasal mucosa. *Laryngoscope.* 1999; 109: 208-211.

[34] Chaundhry AP, Hampel A, Gorlin RJ: Primary melanoma of the oral cavity. *Cancer.* 1958; 11: 923-928.

A Method to Estimate LET-RBE on Cell Killing for Unknown Heavy-ion Particles

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Abstract

The LET-RBE spectra were investigated using cultured V79 cells by accelerated heavy ions. Cells were exposed to ^{3}He-, ^{12}C-, and ^{20}Ne-ion beams at HIMAC, the Medical Cyclotron at NIRS, and RRC at RIKEN with an LET ranging over approximately 10-500 keV/μm under aerobic conditions. Cell-survival curves were fitted by equations from the linear-quadratic model to obtain survival parameters, and the RBE values were analyzed as a function of LET. The RBE increased with LET, reaching a maximum at around 200 keV/μm, then decreased with a further increase in LET. Clear splits of the LET-RBE spectrum were found among ion-spices. The LET-RBE spectra were fitted by a newly contrived equation that including three parameters: L_p, A, and W. The parameters will indicate a LET that gives a maximum RBE, a related value to maximum RBE, and indicates the width of the peak of RBE, respectively. It is also found that the parameters can be defined as functions of atomic numbers of the accelerated ions. At a given LET, the RBE-value for lighter ions was higher than that for heavier ions at lower-LET region. The LET that gives maximum RBE shifts to higher LET for heavier-ions, and the maximum values of the peak of RBE decreased with the atomic number of the irradiated ions.

Introduction

The Heavy Ion Medical Accelerator in Chiba (HIMAC) was constructed at the National Institute of Radiological Sciences (NIRS), Chiba, Japan, in 1993 to perform advanced radiotherapy treatment of cancer[1], [2]. Clinical trials were also started using carbon-ion beams in June 1994, and over 3100 patients had been treated with HIMAC carbon-ion beams by 2007. For a requirement of pre-clinical radiobiological studies and the cooperative research projects in radiobiological field, a great numbers researchers visit HIMAC and huge number of data were obtained by researchers inside and outside NIRS including overseas. HIMAC is also available for scientific experiments, such as medical sciences, physics, radiation biology, and so on. The main subjects for radiobiological studies at HIMAC are studies concerning radiation therapy using heavy-ion beams. However results from the radiobiological studies are applicable for estimating radiobiological effects in a field of radiation protection study for the space, where the most biologically effective radiation is HZE beams.

The relative biological effectiveness (RBE) is one of the most important parameters in determining the biological effectiveness of heavy-ion beams. An accurate knowledge of the RBE was required at HIMAC when heavy-ion beam for cancer therapy will be started. RBE is roughly a simple function of LET, which is the rate of energy deposition in the linear dimension. However the detail and the suitable RBE for cancer therapy is not known, because there are big differences between low- and high-dose region, alternated by hypoxia, discrepancies among particles and by biological end-points. LET indicates the rate of energy deposition in the linear dimension of the absorbing material. There are differences in the radial energy deposition densities for

beams of the same LET among accelerated ion species because of a difference in their electric charge and velocity. This distribution of different track structures of the ionization density may produce different radiobiological effects on cells. However, there are few systematic biological data on the RBE and the LET of heavy ions, because it is usually difficult to expose many biological materials with the same exposure system under the same biological condition.

When we design a therapeutic ion beam, we must know biological effectiveness of the beam. However the LET and ion spices of the beam at defined depth in the body, the physical characteristics of the beam are very complex, because of the nuclear fragmentation of projectile ion and mixture of beams having different LETs to produce a spread-out Bragg peak. To know the RBE for those all ion spices at all radiation doses (or cell survival levels) and all LETs in the beam through biological experiments.

Only a data show here is cell killing on V79 cells as determined by a loss of colony-forming ability, and please see previous publication [5] for HSG cells that has used at HIMAC beam design. The data covers several ion-species, lighter-ions and heavier-ions than therapeutic carbon-ions. We will discuss the LET dependency of cell killing in an intermediate LET region (approximately 10-500 keV/μm) as well as the difference in the RBE spectra among the accelerated ion species. Also we will introduce a method to estimate biological effectiveness of heavy ions as a function of ion species and LETs. In addition, we will discuss possible method to estimate the biological effectiveness to all fragmented beams that have not measured biological experiments.

Experiments

1. Facility and Ion Beams

We exposed cells to ^{3}He-, ^{12}C-, and ^{20}Ne-ion beams. The exposures were carried out at the HIMAC, the medical cyclotron (NIRS-MC) at NIRS, and the ring cyclotron (RRC) facility at the Institute of Chemical and Physical Research (RIKN). The exposure systems at HIMAC, NIRS-MC and RRC were basically the same, and all the beam performance has confirmed by physics group of NIRS. An X-ray machine (Model Shinai-7, Shimadzu Co., Tokyo; 200 kVp, 20 mA, W-target, 0.5-mm aluminum + 0.5-mm copper filter) was used for obtaining the reference survival curves for RBE.

Dosimetry and LET determination at those facilities has previously reported[3][4][5]. Briefly, the dose rates of the beam were measured with a calibrated parallel-plate ionization chamber and/or a plastic scintillation counter at the sample position. A monitoring ionization chamber was placed upstream of the sample. The ratios between the monitor and the calibrated chamber were measured to determine the beam intensity at the sample position for the same ion. The exposure doses were automatically determined by a computer-aided irradiation system by integrating the output current from the monitor chamber.

The accelerated energies of beams used in our experiments were ranging from 12 MeV/u to 400 MeV/u. The LETs at the sample position were selected by changing the accelerated energy of the ion beam and adjusted by using an adequate thickness of aluminum or plastic (Lucite) absorbers[3]. For the experiment at higher-LET beams, we chose as possible as lower energy beam, however we also used some absorbers to select a LET values. Thus secondary ion beams generated in the absorbers cannot be avoided. The most affective ion in secondary beams at carbon experiments is a helium-ion with a LET of several keV/μm. The contribution of the absorbed dose from secondary ions was less than 2 %, as estimated from data obtained by a carbon 290 MeV/u carbon-ion beam near the end of its penetration[6][7]. For the other beams, there are no measurement of the fluence, dose, and LETs of secondary particles by a certain physical experiments. However we can roughly estimate the contribution of the dose from secondary beam by the dose at down stream of the penetration depth of each Bragg-peak. The values were less than 5% for all experiments. The dose would be smaller for beams having shorter penetration ranges than the estimated range.

TABLE 1. Ion Beams Used and possible LET

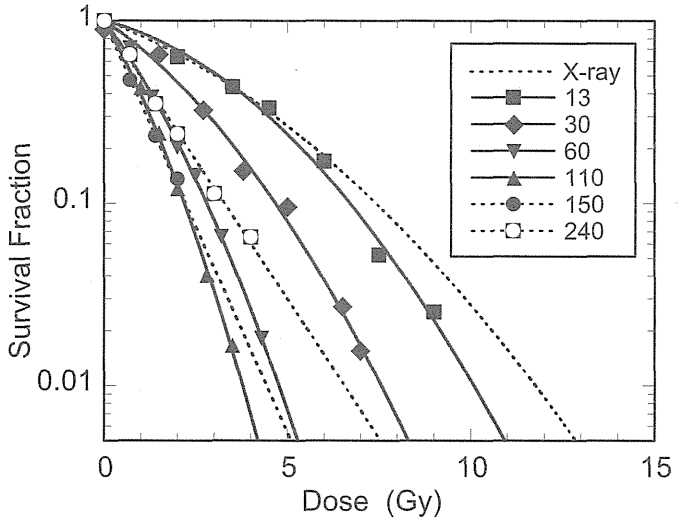
Ion	Energy in vacume (MeV/u)	LET_{min} # (keV/μm)	LET_{max} # (keV/μm)	Institute	Facility
^{3}He	6	28	90	NIRS	Cyclotron
^{12}C	6	250	500	NIRS	Cyclotron
^{12}C	135	21	250	RIKEN	RRC
^{12}C	135/290/350/400	21/13/12/11	250	NIRS	HIMAC
^{20}Ne	135	58	400	RIKEN	RRC
^{20}Ne	135/230/400	58/41/30	400	NIRS	HIMAC

minimum LET for each beam, and possible maximum LET at cell experiments.

2. Cell Culture and Survival Curve Fitting

Chinese hamster V79 cells cultured in Ham's F10 medium supplemented with 15% fetal bovine serum, 0.5 mg/ml Heart Infusion Broth (238400, Difco), and 100 U/ml penicillin and 100 μg/ml streptomycin was used. Cells were harvested by trypsinization, and seeded in dishes were cultured for about 1 day at 37°C in a 5% CO_2 incubator prior to exposure. After exposure, the cells were harvested by trypsinization, and re-suspended in a flesh medium. The numbers of cells in the suspension were counted by a particle counter, diluted with the medium, seeded in three 6-cm culture dishes at approximately 100 expected survivors per dish, and then incubated in an incubator for 6 days. The colonies in the dishes were fixed and stained. Colonies consisting of more than 50 cells were counted under a stereomicroscope as the number of viable cells. The plating efficiencies were greater than 80%. The α and β parameters were obtained from survival data plots by curve fitting using the LQ equation; $SF = \exp(-\alpha D - \beta D^2)$, by using computer programs. The D_{10} values were obtained from the α and β parameters from each survival data set.

Examples of survival curves were shown in Fig. 1. The curves for low-LET radiation showed a gentle curve with large shoulders. The curves become steeper and the shoulder was reduced with increasing of the LET. Gentle curves without shoulder were found at high-LET region. The survival curves for a lower-LET beam were well fitted by the LQ equation, and the survival curve parameters for X-rays; D_{10}, α, and β, were 7.07 Gy, 0.184 Gy^{-1}, and 0.0200 Gy^{-2}, respectively. When cells exposed to high-LET beams, data fitted well by the equation without the β term (or $\beta = 0$), because the curves were linear exponential. The curves were steepest and had no shoulder at LET 150 keV/μm or more, and the slope changed gradually with father increasing of the LET. Numerical data of survival parameters including other cell lines than V79 cells are reported previously [5] together with physical parameters of the beams (E, LET, LET_{100} and Z^{*2}/β^2). The RBE values were calculated as the ratio of the D_{10}s to that of X-rays. RBEs for different LET beams compared to X-rays were obtained for all the beams tested.



<Fig.1> Survival Curves for V79 Cells Exposed to Carbon Ions and X-rays. LET values of ion beams are indicated in the figure in keV/μm unit.

Analysis

1. Fitting of LET-RBE Curve

An experimental equation of LET-RBE relationships as a function of LET was investigated. The equation can be divided into two parts, and the relationship is expressed by using a composite function of the components. The first part (C1) describes a simple decreasing component of RBE with the LET, and the second part (C2) describes a peak of the RBE at a defined LET. The first part is expressed as;

$$C1_{(L)} = 1 / \mathrm{sqrt}\{(L/L_p)^2 + Q/L + 1\},$$

where L is the LET value of the ion-beam, L_p is an LET that shows the inflection point of LET-RBE relationship, and Q is a parameter that defines the shape of the curve at inflection point. The second part is expressed as;

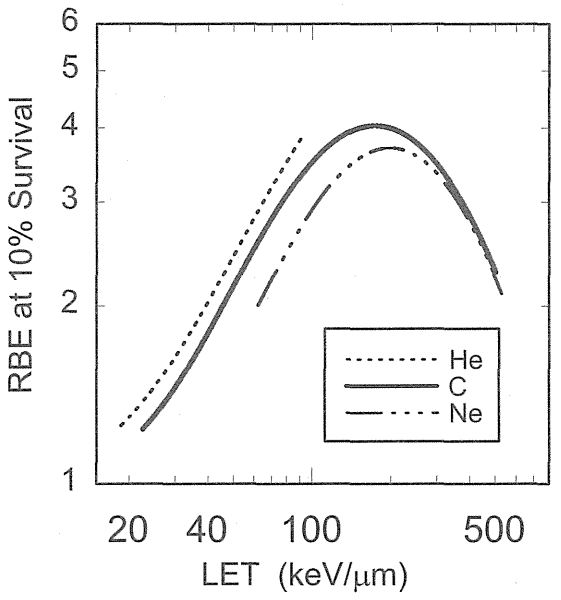
$$C2_{(L)} = A \exp\{ -\ln(L / L_p)^2 / W \},$$

where A is the maximum magnitude of the RBE, L_p is the LET that gives maximum magnitude of the peak in the part, and the W is the width of the peak of RBE. The L_p in C1 and C2 must be different parameter, but power of the C2 is major at around L_0. Also, Q can be negligible by the same reason. Here, we made the L_p of the C1 and C2 to be the same and set $Q = 0$, to reduce the number of the parameters. Finally, here we used an equation;

$$RBE_{(L)} = 1 / \mathrm{sqrt}\{(L / L_p)^2 + 1\} + A \exp\{-\ln(L / L_p)^2 / W\},$$

to analyze the LET-RBE relationship. Calculations were performed by a fitting method using a computer program to minimize the weighted residuals.

The LET-RBE curves were determined using method described above for ^{3}He-, ^{12}C- and ^{20}Ne-ions with the LET ranging 18.6 - 90.8, 22.5 - 502, and 62.1 - 693 keV/μm, respectively, and the results were shown in Fig. 2. The LET-RBE spectra for all ion beams include ^{3}He-ion could be fitted with the fitting equation, and the values of the fitting parameters could be obtained.



<Fig.2> Fitting of RBE as a Function of LET for V79 Cells Exposed to ^{3}He-, ^{12}C- and ^{20}Ne-Ion Beams (each data point not shown).

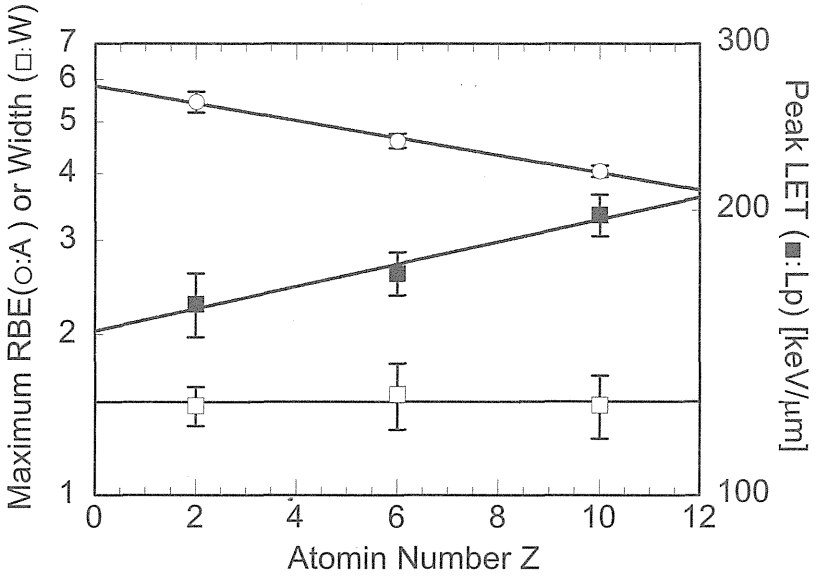
The spectra for those ions were different by the ion species especially in the low and middle LET range (<200 keV/μm), the RBEs showed different values for three different beams (^{3}He > ^{12}C > ^{20}Ne) at the same LET. The RBE spectra for ^{3}He-ion beams start to increase in a lower LET region compared to the other ion beams and reached a larger RBE (~ 4.0) at 90 keV/μm, but didn't showed a maxima. A peak RBE (3.56) was found at 88.3 keV/μm for a ^{3}He-ion beam by a similar experiment[8][9]. The depth-width of the Bragg peak for ^{3}He-ion beam is too narrow to expose a whole cell with a traversal having the same LET and the same dose rate. This means that the energy would be deposited at different LET and dose rates in a cell. The RBE may increase further more at higher LET of ^{3}He-ion, and it could be estimated to reach ~6 by the calculation. The maximum RBE values were found at around 200 keV/μm for ^{20}Ne-ion, and at around 150 keV/μm for ^{12}C-ion.

The difference in the RBE due to the ions is clear in lower-LET region up to 200 keV/μm (Fig. 2), where complete data sets for those three ions exist. For instance, the RBEs were, 3.3, 2.8 and 2.2 at 70 keV/μm for ^{3}He-, ^{12}C- and ^{20}Ne-ion, respectively. In the other word, the LET that gives 3.0 for the RBE of ^{3}He ions was 65 keV/μm, and that for ^{12}C- or ^{20}Ne-ion were at around 77 or 105 keV/μm. This means that to give the same radiobiological effectiveness for ^{12}C- and ^{20}Ne-ion beams to ^{3}He-ion beams, 1.2 or 1.6 times higher LET is required, respectively. There are considerable data[10][11][12] demonstrating such differences in the biological effectiveness of different ion species at the same LET. There is also a theoretical analysis[13] that predicts a difference between the LET-RBE spectra for different ions.

2. Fitting Parameters and Atomic Number

The LET-RBE relationships for ion-beams tested were plotted by a fitting method as described above. In general, the RBE increased with LET, showed peaks at around 100-200 keV/μm, and then decreased with LET. The LET-RBE spectra are different for the different ion spices. The LET-RBE curves are clearly different for the different ion beams. We thought that here must be a relationship between the parameters of the LET-RBE curves and atomic number of the accelerated ions, and the parameters *Lp*, *A* and *W* of LET-RBE curves were plotted as a function of atomic number of the ions (Fig. 3). The Lp increased and the A decreased exponentially with the increase of atomic number, and *W* was a constant. The relationship could be expressed as ;

$Lp = 149 \cdot \exp(0.0271 \cdot Z)$, with r = 0.985,
$A = 583 \cdot \exp(-0.0373 \cdot Z)$, with r = 0.997, and
$W = 1.49$.



<Fig.3>. Parameters of LET-RBE Fitting Equation as a Function of Atomic Number of the Accelerated Ion (Z). The parameters are LET that gives the maximum RBE (L_p), amplitude (A) of the peak of RBE, and the width of the peak (W) of RBE.

Conclusion

We obtained LET-RBE spectra for killing of V79 cells exposed to different ion beams. At a given LET, the RBE-value for lighter ions was higher than that for heavier ions at lower-LET region. The LET-RBE relationship could fitted by a newly contrived equation that including three parameters; L_p, A, and W. It is also found that those parameters can be defined again as functions of atomic numbers of the accelerated ions. The LET of the maximum RBE (L_p) shifts to higher LET values for heavier-ions, amplitude (A) of the peak of RBE decreased with the atomic number of the irradiated ions, and the width of the peak (W) was a constant.

Using those parameters, we are possible to estimate RBEs to the beams at any LET and any ion spice that has not been measured the survival data biologically. Together with physical measurement of the fragmented beam i.e. components in total beam including atomic numbers and it's LET spectrum, we may possible to estimate total/average RBE of the beam. This means we may possible to estimate biological effectiveness to design further therapeutic beams with high accuracy.

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References

[1] Tsujii H *et al* (2007) Clinical Results of Carbon Ion Radiotherapy at NIRS, J Radiat Res 48; A1-A13.

[2] Torikoshi M *et al* (2007) Irradiation System for HIMAC, J Radiat Res 48; A15-25.

[3] Kanai T *et al* (1993) Dosimetry and measured differential W values of air for heavy ions, Radiat Res 135; 293-301.

[4] Kanai T *et al* (1999) Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy, Int J Radiat Oncol Biol Phys 44; 201-10.

[5] Furusawa Y *et al* (2000) Inactivation of aerobic and hypoxic cells from three different cell lines by accelerated ^{3}He-, ^{12}C- and ^{20}Ne-ion beams, Radiat Res 154; 485-96.

[6] Matsufuji N *et al* (2003) Influence of fragment reaction of relativistic heavy charged particles on heavy-ion radiotherapy, Phys Med Biol 48; 1605-23.

[7] Matsufuji N *et al* (2005) Spatial fragment distribution from a therapeutic pencil-like carbon beam in water, Phys Med Biol 50; 3393-403.

[8] Folkard M *et al* (1996) Inactivation of V79 cells by low-energy protons, deuterons and helium-3 ions, Int J Radiat Biol 69; 729-38.

[9] Belli M *et al* (1992) Direct comparison between protons and alpha-particles of the same LET: II. Mutation induction at the HPRT locus in V79 cells, Int J Radiat Biol 61; 625-9.

[10] Blakely EA *et al* (1984) Heavy-ion radiobiology: Cellular studies, in: J.T. Lett (Ed.), Advances in Radiation Biology, Academic Press, New York, pp. 295-389.

[11] Barendsen GW (1968) Response of cultured cells, tumors and normal tissues to radiations of different linear energy transfer, In: M. Ebert and A. Howard Eds, *Current Topics in Radiation Research*, North-Holland Publish Co, Amsterdam, pp. 293-356.

[12] Wulf H *et al* (1985) Heavy-ion effects on mammalian cells: Inactivation measurements with different cell lines, Radiat Res 8; S122-34.

[13] Scholz M and Kraft G (1994) Calculation of Heavy Ion Inactivation Probabilities Based on Track Structure, X Ray Sensitivity and Target Size, Radiat Prot Dosim 52; 29-33.

Design and Operation of HIMAC Facility

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Abstract

The heavy-ion medical accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS) was designed as the world's first medical dedicated heavy ion accelerator complex. Although the common requirements at that time included enough high potential for the future research, the system adopted established principles, structures and devices, thus assuring that enough stability and reproducibility were realized. The use of new challenging technologies was avoided as much as possible. As a result, over 5000 cancer patients have successfully been treated by HIMAC since 1994. We report the status of the recent operation of HIMAC.

Outline of the HIMAC facility

1. Origin of requirement

In order to treat a deep-seated tumor by radiotherapy (RT), it is important to decrease the damage to normal organs surrounding the tumor as low as possible level. The good localized physical dose distribution given by charged particles, especially heavy ions, has been known since the 1940's. In addition, the pioneering work by the Lawrence Berkeley Laboratory, University of California (LBL; the present abbreviation is LBNL) and many biological experiments showed another promising advantage of heavy ion radiotherapy for a deep-seated tumor (HI-RT), i.e. a good relative biological effectiveness (RBE) even for radio-resistant tumors. This advantage comes from the high linear energy transfer (LET) of heavy ions.[1] The first clinical trial of HI-RT was carried out at LBL in the 1970's accompanied with much difficulty in the production of a relativistic high-energy heavy ion beam.[2] (Note: Although the helium ion is a heavy ion, the old He-RT with low energy is classified as a low-LET particle like a proton. So it has been excluded this review.) However, LBL had to break off the clinical trials due to the closure of the accelerator facility, Bevalac, which had been intended for fundamental physics studies. The clinical verification of advantages of HI-RT was kept waiting for a new medical dedicated facility. There were several projects to construct a new medical dedicated facility and to start clinical trials, in the USA,[3] Europe, and Japan in the 1980's. However, only the Heavy-Ion Medical Accelerator in Chiba (HIMAC) was constructed in 1993.[4] A detailed historical review of the European activities, which included the European Light Ion Medical Accelerator project (EULIMA), has been given in Ref. [5].

Although there are historically various beam-delivery systems,[6] the present methods to obtain a large uniform irradiation volume from the pencil shaped and mono-energetic heavy ion beam are roughly divided into two categories shown in Fig. 1.

The first category includes a wobbler method which was developed at LBL and has been utilized for daily clinical treatment at HIMAC.[7] All of the clinical results in Section I.A were obtained by this irradiation method. The system consists of a pair of orthogonal bending magnets and a beam scatterer to spread the beam size in the lateral direction and it is used in association with a ridge filter as a range modulator. This method requires a beam collimator and a range compensator and both items are usually patient-specific hardware. The disadvantage is that an unwanted dose will be deposited on the entrance path of target; that dose is of the same level as the dose to the

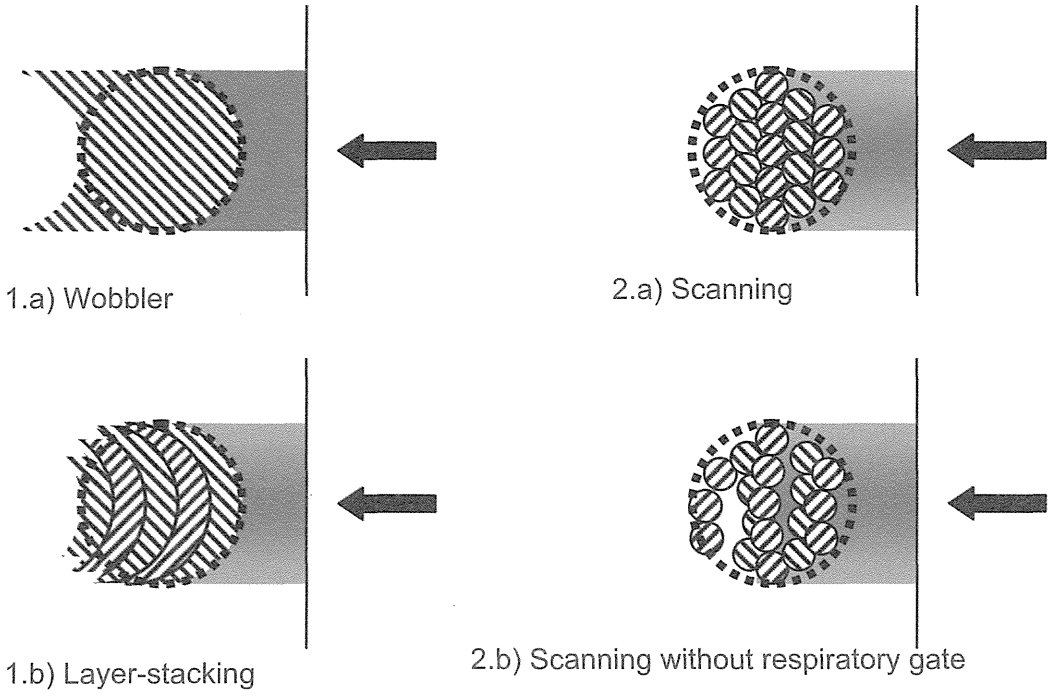

Fig. 1. Two categories of irradiation methods;
1) wobbler method, 2) pencil beam scanning method.

target volume. In order to reduce this deposited dose, the layer-stacking wobbler method has been utilized for several tumor types at HIMAC.[8]

The second category includes pencil-beam scanning methods, such as spot scanning and raster scanning. The first spot-scanning system for proton radiotherapy (p-RT) was developed at NIRS.[9] The Paul Scherrer Institute (PSI) in Villigen, Switzerland has routinely utilized the one-dimensional spot-scanning method with the movement of the patient couch for pion RT at first, then for p-RT.[10] For HI-RT, the Gesellschaft fur Schwerionenforschung (GSI) in Darmstadt, Germany has developed the three-dimensional raster-scanning method with variable beam-energy acceleration, and is utilizing it for daily clinical treatment.[11] This method realizes a better dose distribution without an unexpected dose on normal tissues. In addition, the beam intensity efficiency is better than the wobbler method, and patient-specific hardware is not necessary. However, the most acute disadvantage is that the pencil-beam scanning method is extremely sensitive to organ motion during treatment. This is one reason why NIRS aborted its own developed scanning method and adopted the wobbler method at HIMAC. Since it is difficult to make a uniform dose distribution in a trunk organ by respiratory-gated irradiation with a reasonable margin, acceptable irradiation efficiency, and reliable quality assurance, the pencil-beam scanning methods have mostly been utilized for treatments of head and neck tumors only. The development on the respiratory gated scanning method is now a hot topic in this field,[12,13] even for p-RT.

The beam diagnosis system is one of the most important elements of the irradiation technique. A gas ionization chamber (IC) is usually used as an on-line dose monitor during the treatment. The ionization in the IC is proportional to the energy transfer from charged particles. Although the calibration at the same conditions as used during treatment is necessary, the IC can correctly measure the total integrated dose during the irradiation. On the other hand, the time response of the IC is not so fast. The time structure of the beam is not clear from measurements of the IC. The biological effectiveness depends on the dose rate, in principle. If the time structure has a very steep peak, careful account must be taken of the biological dose distribution.

The role of an accelerator is simply to supply a heavy ion beam with enough intensity and energy. However the primary requisite of a medical accelerator strongly depends on each irradiation method. The wobbler method allows

wide margins for beam quality. On the other hand, the pencil-beam scanning methods require a precisely known beam energy, position, emittance, and a good intensity stability.

2. Design concept and original specification of HIMAC

In early 1980's, the mortality from cancer became the first cause, and the number of cancer deaths in 1990's was estimated to be approximately 300 thousands in Japan. Because the weight of the advanced aged people was expected to become heavier in the composition of the population. Japanese government required development of new treatment methods for the cure of cancer patients to hold good for the "Quality of Life" of the patients after the treatment. The heavy-ion medical accelerator in Chiba (HIMAC) project had been promoted by the Government as one of the projects of "Comprehensive 10 year Strategy for Cancer Control" which came into operation in 1984.

Since HIMAC was designed as the world's first medical dedicated heavy ion accelerator complex, the requirements for the medical use of heavy ion beams were not known well. All of researchers, i.e., medical doctors, biologists, and physicists expected enough high potential for the future research. For ion species, Si or Ar ions were considered giving the highest oxygen gain factor. The common requirements at that time were as follows for ion species between He and Si. The required maximum range and irradiation field size were 25 cm and 15 x 15 cm, respectively. The maximum biological dose rate was expected to be 5 Gy/min. In order to obtain a better dose distribution by the multi-direction irradiation, two horizontal and two vertical irradiation ports were desired. A maximum energy of 800 MeV/u was required for ions with a charge-to-mass ratio of 1/2. That would give a residual range of 30 cm in water for Si, and it was possible to make the irradiation range 25 cm with the wobbler method. The accelerator complex consisted of two synchrotrons,[14] a series of two injector linacs,[15] and two ion sources.[16] The two synchrotron rings were installed in the upper and lower underground floors and were operated independently of each other except for the alternating injection and excitation of magnets. A patient's positioning system, and a treatment planning system are also important. The details of such systems have been described in references [17] and [18].

The scope of future developments for HIMAC was expected to include the development of the storage for radioactive isotope beams (RIBs), the formation of quasi-continuous beams (QCBs) and so on. QCBs were demonstrated, however they are not necessary now. RIBs are still being researched,[19] and they have not been utilized for clinical trials. The HIMAC system adopted established principles, structures and devices, thus assuring that enough stability and reproducibility were realized. The use of new challenging technologies was avoided as much as possible. In summary, the requirements of the range, field size, and dose rate were very close to the present day requirements.

One of the most important aims of the control of HIMAC facility was to obtain enough stable beams with good reproducibility. The control system was designed under the policy of the passive and static ways. The active feedback system is not used as possible. All of the devices of the accelerator components are made controllable through a computer system. All of the parameters and measured values are digitalized and can be saved as a parameter file after beam tuning. Under the well-known condition, since the parameter set up can be obtained automatically, it is only needed for an operator to select the parameter file and to turn on the start-up button. In order to realize the same beam trajectory with the same magnetic field, all transport magnets are set towards the well-established excitation pattern. Although this procedure takes several minutes, the merit to obtain a good reproducibility. This policy is also effective for the quality assurance and control.

Operation of HIMAC

1. Status of the daily operation

In a typical weekly schedule of beam time, the beam tuning starts up on Monday. Patients are treated during the daytime of weekdays. Every night and on weekend, beam time is available for general experiments. The accelerator facility is shut down in the night of Saturday or in the morning of Sunday. The maintenance and the

research development without the beam are carried out in the daytime of every other Monday. The combination of two synchrotrons to form the quasi-continuous beam was developed, but it's not necessary for the daily treatment. Almost experimental users also preferred to use longer machine time or more various ion species instead of the continuous beam. Therefore, in order to use the two synchrotrons more effectively, the time-sharing acceleration system of the injector was developed to supply different ion beams to the two synchrotrons simultaneously. All magnets in the beam transport line were replaced for the pulse operation. Another ECR ion source was installed to produce intensive highly charged heavier ions like Fe, Kr, and Xe. The 18 GHz NIRS-HEC ion source has the similar structure as the 10 GHz NIRS-ECR, however the magnetic field and the extraction voltage are improved. As a result, three independent users can use different beams after the lower, upper synchrotrons and the linac.

HIMAC is stopped in two long research and maintenance periods per year. Large modifications or installations were done in these periods. The number of operation days is normally 250 days. About 180 days are occupied by the treatment. Fig. 2 shows the statistics of HIMAC operation in the financial year 2008. The injector linac (INJ) was operated for 5774 hours. This operation time includes the beam providing to the synchrotrons and individual experiments with the injector's energy beam. The operation time for the experiment was 884 hours. The upper synchrotron and the lower one (USY & LSY) were also operated for 5713 and 5724 hours, respectively. The operation time for the treatment was 3174 hours by the upper beam transport line and the lower one (UBT & LBT). The operation time for the experiment was 4582 hours too. The users including the treatment received the beam for 8640 hours per year, successfully. The ratio of failure to operation for INJ, USY, and LSY were 0.3 %, 0.2%, and 0.1%, respectively.

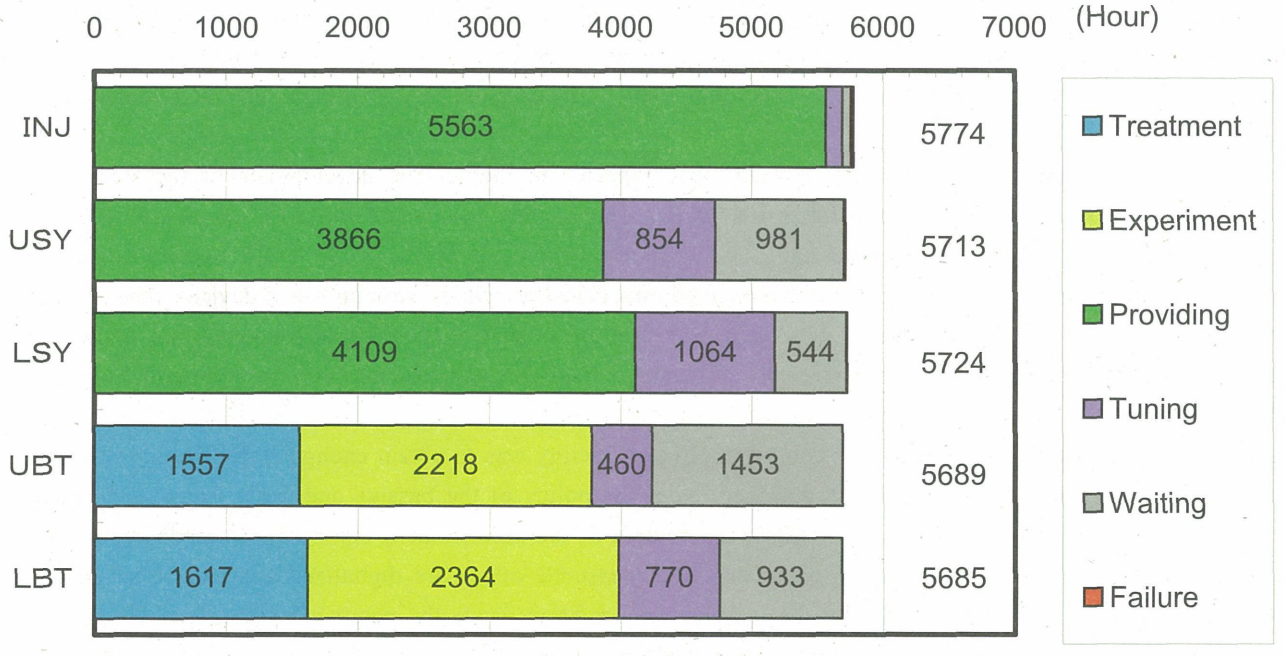

Fig. 2 Statistics of HIMAC operation (FY2008)

Fig. 3 shows the numbers of patient, treatment planning, and irradiation per year. At first, about 1000 irradiations per year were carried out in 1995. But now the total number of irradiation exceeded 9000. Although the capacity of irradiation mainly depends on the patient positioning time rather than the irradiation time, this increasing of irradiations clearly shows the evidence of the stable operation of the facility. On the other hand, the number of troubles of the irradiation system are increased as the number of patients.

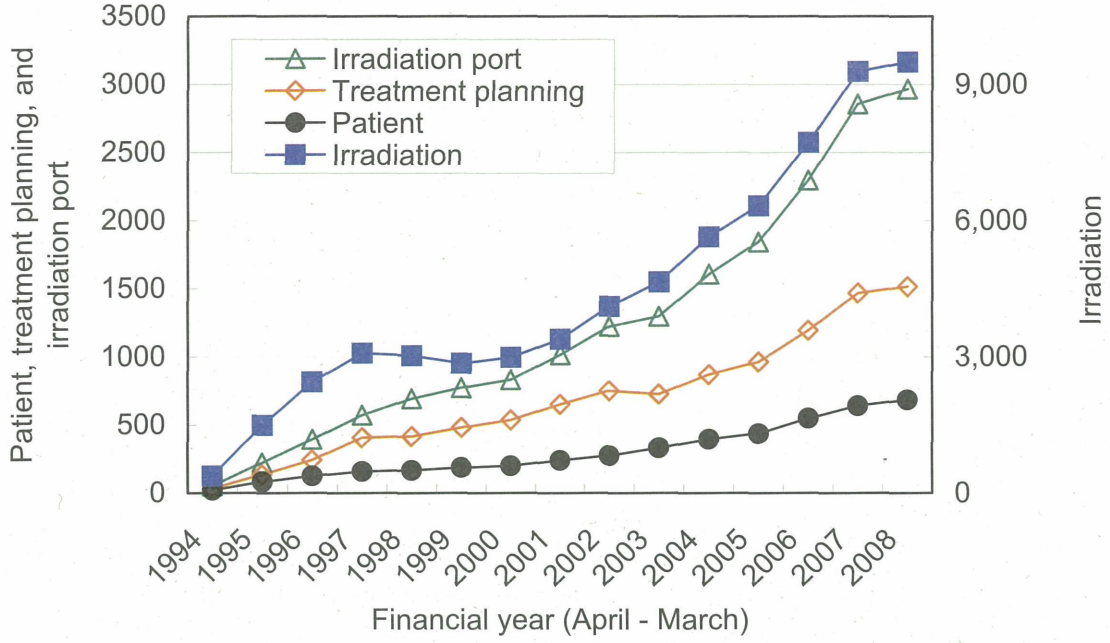

Fig. 3 Increasings of patients, treatment plannings, and irradiations

2. Effort to decrease failures

There are two types of the tendencies of the long-term variation of failures. One example is the case of the 10 GHz ECR ion source. This device's development was not completed at the design stage and it was necessary to improve by the commissioning. Fig. 4 shows the long-term variation on failures that have stopped beam production, or caused an instability. "Serious failures", which stopped the source operation for more than one day, and "Heavy failures", which required more than one hour for recovery, occurred during the early stage of operation. These were mainly due to bags of components, which have been improved. It was possible to recover from "Light failures" by resetting the parameters, or making small corrections, which also increased several years after. Since these are mainly due to aging deterioration, it can be managed by replacing any weak parts before their lifetime. It is also important to consider a reduction in the number of parts in the design. Failures of the klystron-based microwave amplifier account for one third of all the failures. It seems that the

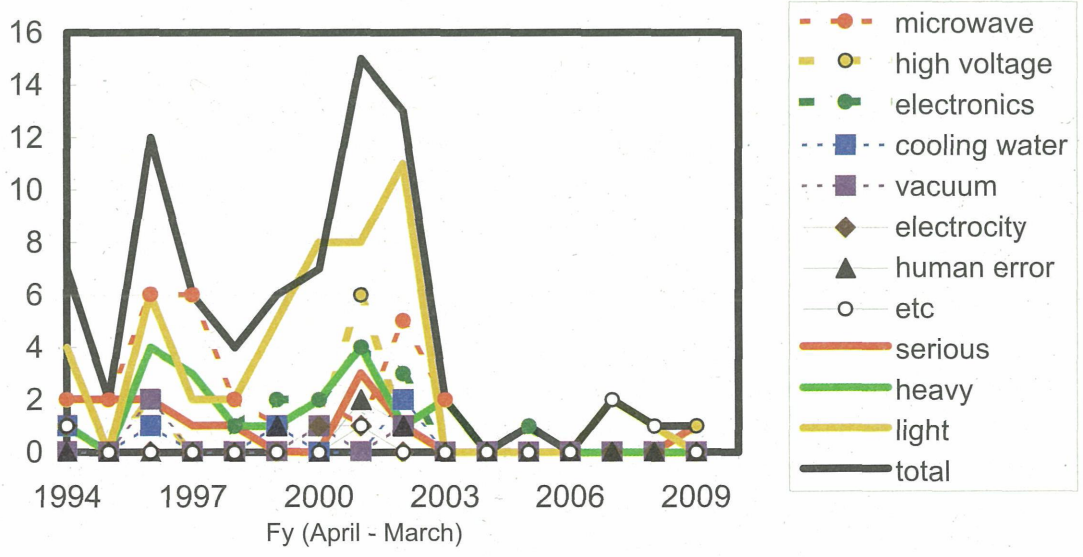

Fig. 4 Failure of 10 GHz ECR ion source

frequency of these failures is over the usual average. Finally, we aborted to use the old amplifier, and developed a new traveling-waveguide tube (TWT) amplifier with NEC microwave Co. Ltd. TWT has a smaller maximum power than that of the klystron. In the case of our microwave guide system, over 1 kW of microwave power is necessary to produce C^{4+} ions, due to the low transmission efficiency. We combined two 700 W TWT for the amplifier. Since the lifetime of TWT is expected to be over 15000 hours, the operational cost becomes cheaper. After we replaced the amplifier on August 2004, no failure has occurred at the microwave. So that, another medical facility, Hyogo, has also been replaced instead of old one. Gunma Univ. has adopted the same device too. Due to these improvements and maintenance, no serious or heavy failure had occurred for 4 years.

An example of another type of the tendencies of the long-term variation of failures is the failures at the irradiation system. If the probability of failures at each device does not change, these failures are proportional to the number of irradiations. In order to decrease such failures, the quality assurance (QA) and control in the daily operation are very important. The QA activity of the irradiation system was described minutely in Reference [20].

It seems failures which are categorized a long-term steady deterioration in the quality of parts are slightly increasing recently. It is the greatest concern that many parts will have more serious situations in near future, i.e., after 20 years since the construction. We believe no one can avoid every failures. When any failures occurred, in case 1; equivalent devices are used in parallel, we can switch the device quickly. In case 2; spare parts are kept, we should exchange the parts. In case 3; other cases, we must repair the failed parts. It's effective to exchange or repair weak parts before becoming serious failures from the routine check.

References

[1] Blakely E A, Ngo F Q H, Curtis S B and Tobias C A, Adv. Radiat. Biol. 11, 1984, 295.

[2] Biological and Medical Research with Accelerated Heavy Ions at the Bevalac, LBL-11220, UC-48, 1980.

[3] Gough R, Alonso J, Eliott T, *et al.*, IEEE Trans. Nucl. Sci. NS-30, 1983, 3067.

[4] Hirao Y, Ogawa H, Yamada S, *et al.*, Nucl. Phys. A 538, 1992, 541c.

[5] Amaldi U and Kraft G, J. Radiat. Res. 48, 2007, A27.

[6] Chu W T, Ludewigt B A, and Renner T R, Rev. Sci. Instrum. 64, 1993, 2055.

[7] Kanai T, Endo M, Minohara S, *et al.*, Int. J. Radiation Oncology Biol. Phys. 44, 1999, 201.

[8] Kanai T, Kanematsu N, Minohara S, *et al.*, Med. Phys. 33, 2006, 2989.

[9] Kanai T, Kawachi K, Kumamoto Y, *et al.*, Med. Phys. 7, 1980, 365.

[10] Pedroni E, Bacher R, Blattmann H, *et al.*, PSI-Bericht, 69, 1989, 1.

[11] Haberer T, Becker W, Schardt D and Kraft G, Nucl. Instrum. Meth. A330, 1993, 296.

[12] Furukawa T, Inaniwa T, Sato S, *et al.*, Med. Phys. 34, 2007, 1085.

[13] Bert C, Saito N, Schmidt A, *et al.*, Med. Phys. 34, 2007, 4768.

[14] Sato K, Yamada S, Ogawa H, *et al.*, Performance of HIMAC. Nuclear Physics A588, 1995, 229c-234c.

[15] Murakami T, *et al.*, Proc. of 18th Intrnl. Linac Conf., Geneva, 1996, 830.

[16] Kitagawa A, Yamada S, Muramatsu M, *et al.*, Rev. Sci. Instrum., 1996, 67, 962-964.

[17] Minohara S, Kanai T, Endo M, *et al.*, Int. J. Rad. Oncol. Bio. Phys. 47, 2000, 1097-1103.

[18] Endo M, Koyama-Ito H, Minohara S, *et al.*, J. Jpn. Ther. Radiol. Oncol. 8, 1996, 231-238.

[19] Kanai T, Endo M, Minohara S, *et al.*, Int. J. Radiation Oncology Bio. Phys. 44, 1999, 201-210.

[20] Torikoshi M, Minohara S, Kanematsu N, *et al.*, Proceedings of NIRS-ETOILE Joint Symposium 2009 on Carbon Ion Radiotherapy, Lyon, France, 136-144.

New Treatment Facility Project at HIMAC

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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 5,000 as of February 2010. The impressive advance of carbon-ion therapy using HIMAC has been supported by high-reliability operation and by the development of accelerator technology. Based on more than ten years of experience with HIMAC, we have proposed a new treatment facility for the further development of therapy with HIMAC. The new facility, as an extension of the existing one, has been designed, and the related R&D work has been carried out. The following descriptions give a summary account of the design study and the related R&D work for this new treatment facility at HIMAC.

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 beams was conducted in June 1994. The total number of patients treated until February 2010 was more than 5,000. Based on more than ten years of experience with HIMAC, we have proposed a new treatment facility toward adaptive cancer therapy [2] with heavy ions, making the one-day treatment of lung cancer possible. Further, the new treatment facility should accurately treat a fixed target, a moving target with breathing and/or a target near a critical organ. For these purposes, a 3D-scanning method with a pencil beam is employed in the new treatment facility. A phase-controlled rescanning (PCR) method [3] has been proposed and studied, especially for treating a moving target. A rotating gantry with the PCR method [4] is also employed in order to reduce the patient's load, such as face-downward position during patient positioning, and to increase treatment accuracy for a tumor near a critical organ through multi-field optimization [5]. In addition, we have designed the beam-delivery system, the rotating gantry system, the treatment flow including patient positioning and the facility planning. The related R&D work has also been carried out with HIMAC since 2006. A construction of the facility building will be completed in March 2010. After installing and tuning up the equipment, the 1st patient will be treated in March 2011.

2. Design and R&D works

In HIMAC treatments, we have observed shrinkage of the target size as well as a change in its shape during the entire treatment. In order to keep the sophisticated conformations of the dose distributions even in such cases, it has been required that treatment planning is carried out just before each fractional irradiation, which we call adaptive therapy. For this purpose, 3D scanning with a pencil beam should be employed, because it does not use any bolus and patient collimators, which take a long time to be manufactured. It is also well-known that 3D scanning has brought about a high treatment accuracy in the case of a fixed target [6]. However, this method has not yet been applied to treating a moving target with breathing in practical use. Therefore, we have developed the PCR method to treat a moving target.

2.1 Phase-controlled rescanning method

The new facility should be designed to employ a pencil-beam 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 this purpose, we have proposed the PCR method with a pencil-beam. In the PCR method, rescanning completes the irradiation of one slice during a single gated period corresponding to the phase between the end of expiration and the beginning of inspiration, because the organs are most stable during this gated period. Further, since the average displacement of the target over a single gated period is close to "zero", we can obtain uniform dose distribution even under irradiation of a moving target. The PCR method requires two main technologies: (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.

2.2 Intensity modulation

We have developed a spill control system [7] in order to deliver the beam with intensity modulation, based on improvement of the RF-KO slow extraction method. The core part of this system requires the following functions: (1) calculation and output of an AM signal according to request-signals from an irradiation system, (2) real-time processing with a time resolution less than 1 ms, and (3) feed-forward and feedback controls to realize the extracted intensity as requested. This system allows us to dynamically control the beam intensity almost as required, as shown in Fig. 1.

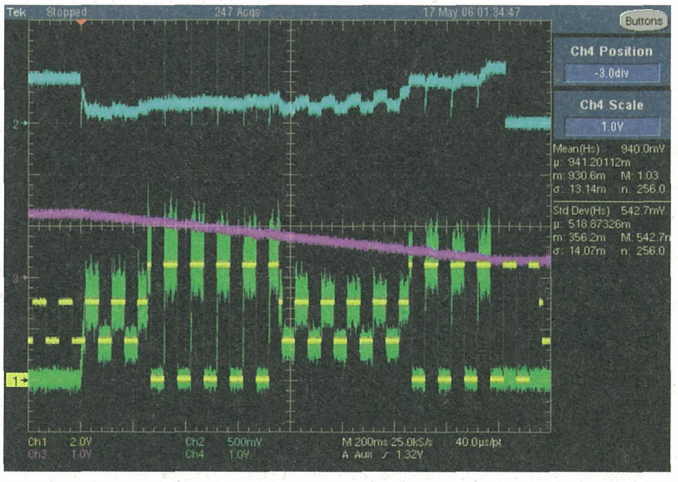

Fig. 1. Time structure of extracted beam obtained by the spill-control system. Spill time structure (green) modulated by request signal (yellow).

2.3 Fast pencil-beam scanning

For the fast pencil-beam scanning, we have developed three key technologies as follows: (1) new treatment planning for raster-scanning, (2) extended flattop operation of the synchrotron, and (3) high-speed scanning magnet.

Raster-scanning has been chosen, instead of spot scanning, in order to save the beam-off period during spot-position movement. With the raster-scanning method, however, it is inevitably necessary to deliver an extra dose to the position between the spot positions. It should be noted that the extra dose is proportional to the delivered intensity. Owing to the high reproducibility and uniformities in the time structure of the extracted beam through the spill-control system, we can predict the extra dose and incorporate its contribution in the treatment planning. Consequently, we can increase the beam intensity and shorten the irradiation time.

On account of a high beam-utilization efficiency of around 100% in the scanning method and an intensity upgrade to 2×10^{10} carbon ions, we can complete single-fractional irradiation of almost all treatment procedures in a single-operation cycle of the synchrotron, This single-cycle operation, which can be realized by using a clock-stop technique in the flattop period, can increase the treatment efficiency especially for respiratory-gated irradiation. Thus we have proposed the extended flattop operation of the synchrotron. In this operation mode, the stability of the beam was tested, and it was verified that the position- and profile-stability was less than ±0.5 mm at the iso-center in 100 s of extended flattop operation. This extended flattop operation can shorten the irradiation time by a factor of 2.

Scanning speed is designed to be 100 mm/ms and 50 mm/ms in the horizontal and vertical directions, respectively, faster by around one order than that in the conventional way [8]. In order to increase scanning speed, we designed a scanning magnet with slits in both ends of the magnetic poles, according to thermal analysis, including an eddy-current loss and a hysteresis loss. The power supply of the scanning magnet was designed for fast scanning, and this consists of two stage circuits: the first stage for voltage forcing by IGBT switching elements and the second stage for the flattop-current control by FET switching elements. Testing showed a maximum temperature rise of around 30 degrees, which was consistent with our thermal analysis

2.4 Scanning experiment

In the first stage, we carried out a fast raster-scanning experiment by using the HIMAC spot-scanning test line [8]. The irradiation control system was modified so as to be capable of raster-scanning irradiation instead of spot-scanning. In the experiment, we adapted the measured dose response of the pencil beam with energy of 350MeV/n, corresponding to a 22-cm range in water. The beam size at the entrance was adjusted to 3.5 mm at one standard deviation. Using a mini-ridge filter, the Bragg peak was slightly spread out to Gaussian shape with a width of 4 mm at one standard deviation. The validity of the beam model and the optimization calculation had already been verified experimentally [9]. In the experiment, the extraction beam rate was highly stabilized during the extended flattop operation, owing to the spill-control system, and we were able to successfully carry out the pencil-beam raster-scanning experiment.

We designed and constructed a test irradiation port for the fast raster-scanning experiment in order to verify the design goal, which was the same configuration as the fixed beam-delivery system adapted to the new treatment facility. The test irradiation port is shown in Fig. 2. In a preliminary test, we delivered irradiation to a target with a spherical shape, 6 cm in diameter, and obtained uniform 3D dose distribution within 10 s even with 10 times rescanning.

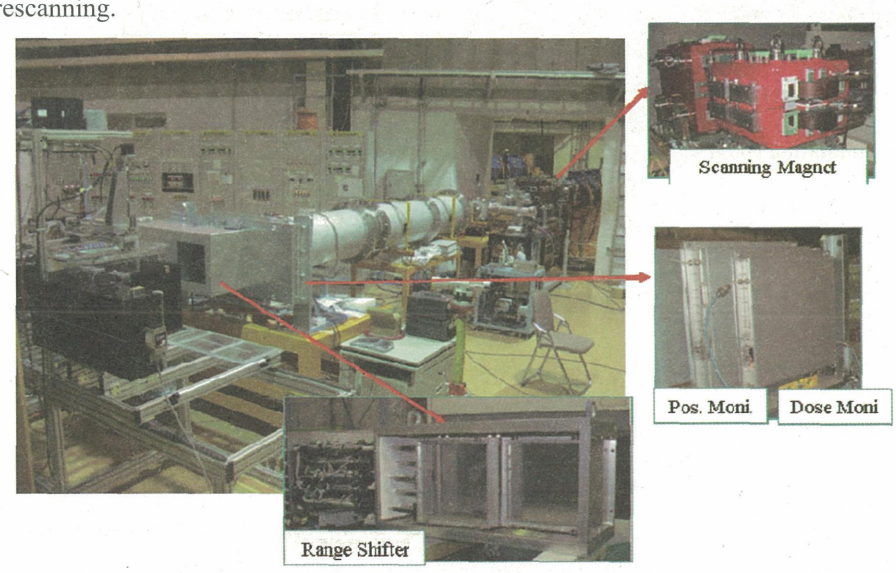

Fig. 2. Photograph of the test irradiation port for the fast 3D scanning experiment.

3. Facility design

The 12C beam will be mainly used for treatments that have been carried out in the existing HIMAC facility. Different ion species will also be employed for the further development of particle therapy at NIRS. In addition, positron-emission beams, such as ^{11}C and ^{15}O, will be used to verify the irradiation area and their ranges in a patient's body. Thus, an R&D study has been carried out in order to obtain positron-emission beams accelerated directly through the HIMAC accelerator [10], instead of using the projectile-fragmentation method. In order to carry out this study in a manner identical to the existing HIMAC treatment, the residual range required has to be more than 25 cm. Thus, the maximum ion energy is designed to be 430MeV/n in the fixed beam-delivery system, corresponding to a residual range of 30 cm in a ^{12}C beam and 22 cm in a ^{16}O beam. The maximum lateral-field and SOBP sizes are 22 cm × 22 cm and 15 cm, respectively, in order to cover almost all treatments with HIMAC. On the other hand, the rotating gantry system employs a maximum energy of 400MeV/n, a maximum lateral-field of 15 cm × 15 cm and a maximum SOBP size of 15 cm in order to be able to downsize the gantry size.

The new treatment facility is connected to the upper synchrotron of HIMAC. In the treatment hall, placed beneath the facility, three treatment rooms are prepared in order to treat more than 800 patients per year. Two of them are equipped with fixed beam-delivery systems in both horizontal and vertical directions, while the other is equipped with a rotating gantry. Two treatment-simulation rooms are also prepared for patient positioning as a rehearsal place, and for observing any changes of target size and shape with x-ray CT during the entire treatment. Furthermore, six rooms are devoted to patient preparation before irradiation. A bird's eye view of the new treatment facility at HIMAC is shown in Fig. 3.

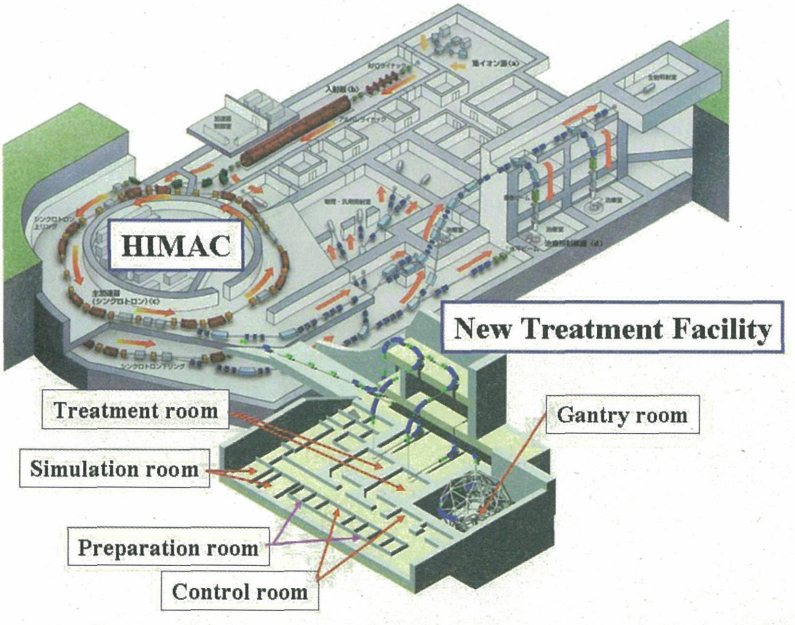

Fig. 3. Schematic view of the new treatment facility and the present HIMAC.

4. Summary

At the HIMAC accelerator complex, beam studies were carried out especially for increasing the irradiation accuracy and treatment efficiency. As a result, we were able to upgrade the performance of the HIMAC accelerator complex. Based on this upgrade, we have proposed a new project for further development of heavy-ion therapy with HIMAC, entailing the construction of a new treatment facility. The new treatment facility

has three treatment rooms: two rooms are equipped with horizontal and vertical beam-delivery systems equipped with a 3D pencil-beam scanning capability, and the other with a rotating gantry with a 3D pencil-beam scanning capability. The beam-scanning irradiation method uses the PCR method with a fast scanning performance. These developments have made continuous successfully progress since 2006. A construction of the facility building will be completed in March 2010. After installing and tuning up the equipment, the 1st patient will be treated in March 2011.

References

[1] Y. Hirao et al., Nucl. Phys. A 538, 541c–550c (1992).

[2] K. J. Halverson et al., Int. J. Radiat. Oncol. Bio. Phys. 21:1327-1336 (1991).

[3] T. Furukawa, T. Inaniwa, S. Sato, T. Tomitani, T. Minohara, K. Noda, T. Kanai, Med. Phys. 34 (3), 1085-1097 (2007).

[4] T. Furukawa, T. Inaniwa, S. Sato, Y. Iwata, S. Minohara, K. Noda, T. Kanai, in these proceedings.

[5] A. Lomax, Phys. Med. Biol. 44:1219-1226 (1999).

[6] Th. Haberer, W. Becher, D. Schardt, G. Kraft, Nucl. Instrum. Meth. A 330, (1993) 296-305.

[7] S. Sato, T. Furukawa, K. Noda, Nucl. Instrum. Meth. A 574, (2007) 226-231.

[8] E. Urakabe et al., Jpn. J. Appl. Phys. 40 (2001) 254.

[9] T. Inaniwa, et al., Nucl. Instrum. Meth B 266 (2008) 2194.

[10] S. Hojo, T. Honma, Y. Sakamoto, S. Yamada, Nucl. Instrum. Meth. B 240 (2005) 75.

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