

Clinical Results of Carbon Ion Radiotherapy at NIRS

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Carbon ions/Charged particles/Dose distribution/RBE/Clinical study.

In 1994 a Phase I/II clinical study on carbon ion radiotherapy was begun at NIRS using HIMAC, which was then the world's only heavy ion accelerator complex dedicated to medical use in a hospital environment. Among several types of ion species, we have chosen carbon ions for cancer therapy because they had the most optimal properties in terms of possessing, both physically and biologically, the most effective dose-localization in the body. The purpose of the clinical study was to investigate the efficacy of carbon ion radiotherapy against a variety of tumors as well as to develop effective techniques for delivering an efficient dose to the tumor. The RBE of carbon ions was estimated to be 2.0 to 3.0 along the SOBP for acute skin reactions. As of August 2006, a total of 2,867 patients had been entered into Phase I/II or Phase II studies and analyzed for toxicity and local tumor response. The results have shown that carbon ion radiotherapy has the potential ability to provide 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 and those with histologically non-squamous cell type of tumors such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. By taking advantage of the biological and physical properties of high-LET radiation, the efficacy of treatment regimens with small fractions in short treatment times has been confirmed for almost all types of tumors in carbon ion radiotherapy.

INTRODUCTION

A structural survey carried out by Japanese Society for Therapeutic Radiology and Oncology (JASTRO) has demonstrated that the number of cancer patients undergoing radiotherapy has been increasing year by year in Japan.¹⁾ Of the total cancer patients of 530,000, roughly 28%, that is, 150,000, have been treated with radiotherapy, with forecasts that this number will continue to rise in the future. The reason is that in recent years the scope of diseases that can be treated by radiotherapy has widened significantly in the wake of the diffusion of such "dose localization irradiation techniques" as stereotactic radiotherapy (SRT), intensity-modulated radiotherapy (IMRT) and particle beam radio-

therapy. They are radiotherapeutic modalities that allow the sparing of normal tissues and facilitate the administration of curative doses to the tumor. In this context, charged particle radiotherapy using proton beams and heavier ion beams, which was first proposed for clinical application by R. Wilson in 1946,²⁾ has been confirmed as being effective in terms of improved local control and less risk of normal tissue damage. In the early 1950s, the clinical use of proton and helium ion beams was initiated in the United States at Lawrence Berkeley National Laboratory (LBNL), paving the way for heavy ion beam radiotherapy starting at the same facility in the 1970s.^{3,4)} At present, particle beam radiotherapy is being performed at about 30 facilities worldwide.

In Japan, the decision was made in 1984 to build the Heavy Ion Medical Accelerator in Chiba (HIMAC) at 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 and was completed by the end of 1993. A year later, in 1994, a Phase I/II clinical study using carbon ion beams generated from the HIMAC was initiated for cancer therapy.

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While the proton accelerator built at Loma Linda University in 1990 was the first proton beam accelerator put primarily into therapeutic service, the HIMAC can claim to be the world's first facility dedicated to cancer therapy using heavy ion beams. The HIMAC has also been operated as a multi-purpose facility available for the joint use of cancer treatment and biological and physical research by both Japanese and overseas researchers.

Carbon ion radiotherapy now enters its 13th year at NIRS, and a substantial amount of evidence has been accumulated with the support of many contributing members, both inside and outside the Institute, demonstrating the clinical efficacy of carbon ions on various types of malignant tumors. One of the most important objectives in these endeavors has been to determine, in particular, the validity of hypofractionated and accelerated radiotherapy. At the end of 2003, the Institute was successful in obtaining approval for a program called Highly Advanced Medical Technology (HAMT) for its Heavy Particle Radiotherapy from the Ministry of Health, Labor and Welfare. This was an important landmark for broadening the scope of diseases that could be treated with, and would respond to carbon ion radiotherapy. In this manner, heavy particle radiotherapy has won for itself a solid place in general medical practice, with the next target being the approval of this therapy under the National Health Insurance System in Japan.

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

CHARACTERISTICS OF CARBON ION RADIOTHERAPY

Carbon ion beams share with proton beams the property of forming a high dose region known as a spread-out Bragg peak

(SOBP) in the body. In addition, carbon ion beams deliver a larger mean energy per unit length of their trajectory in the body (Linear Energy Transfer: LET) than proton and photon beams.⁵⁻⁷⁾ This unique property entails a high local tumor control when used in radiotherapy. As a result, carbon ion beams are described as a high-LET radiation, similarly to neutron beams. 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 entrance in the body with increasing depth to reach a maximum in the peak region (Fig.1). This property is extremely advantageous from a therapeutic viewpoint, because the biological effect of carbon ion beams increases as they advance deeper to the tumoring region. This opens up a promising potential for their highly effective use in the treatment of intractable cancers that are resistant to photon beams.

In view of these unique physical and biological properties of carbon ion beams, it is theoretically possible to perform hypofractionated radiotherapy using significantly smaller number of fractions than has been used in conventional radiotherapy. Experiments with fast neutron beams, which have the same high-LET components as carbon beams, have demonstrated that increasing their fraction dose tended to lower their relative radiobiological effectiveness (RBE) for both tumor and normal tissues.⁸⁾ In these experiments, however, the RBE for the tumor did not decrease as rapidly as the RBE for the normal tissues. This experimental result substantiates the fact 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.^{9,10)} They have provided the biological evidence for the validity of the short-course hypofractionated regimen in carbon ion radiotherapy.

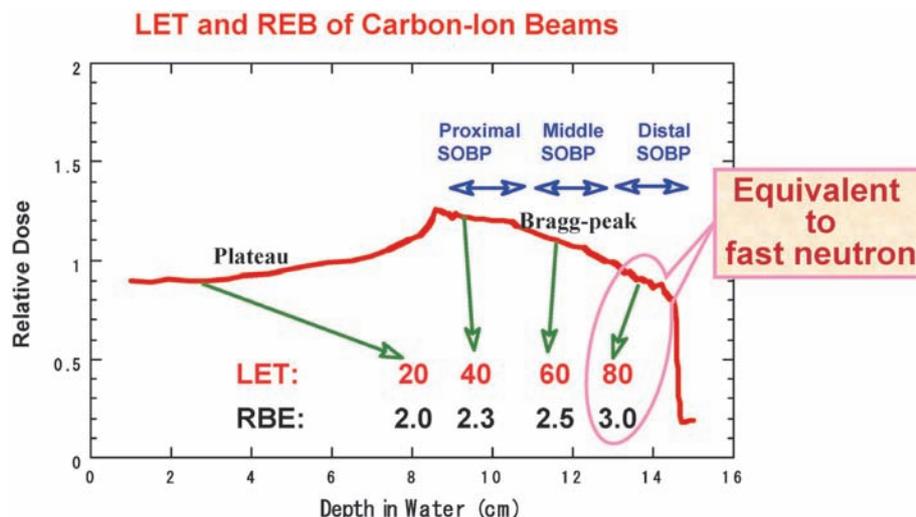


Fig. 1. LET & RBE values used in clinical study (Carbon ion, 290MeV, SOBP = 60 mm). The density of ionization increases with depth in the body.

CARBON ION RADIOTHERAPY AT NIRS

Framework for administration of carbon ion radiotherapy

Consistent efforts have been made at NIRS since the beginning to provide carbon ion radiotherapy on an ethically and scientifically sound basis under a number of Committees headed by the “Heavy Ion Radiotherapy Network Committee” as the supreme organ responsible for clinical studies. All clinical study protocols are first prepared by the Planning Teams, then evaluated by the disease-specific Subcommittees, and finally approved by the Network Committee after investigation by the Ethical Committee. An Evaluation Committee is appointed to deliberate on the validity of whether the individual clinical studies should be continued, and the results of all clinical studies are submitted to the Network Committee whose sessions are invariably held in public.

As described earlier, carbon ion radiotherapy was approved as a HAMT in 2003, available under the title of “Heavy Ion Radiotherapy for Solid Cancers.” The HAMT has been designed to respond to the development of novel medical technologies and to meet the diversifying needs for

medical treatment, permitting Specific Medical Institutions under the National Health Insurance System to offer an advanced medical treatment and thereby enable them to practice both the HAMT and general care within the National Health Insurance System. Under this scheme, care providers are able to charge their patients a special fee for HAMT 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 HIMAC construction costs, personnel costs, the costs for the materials used for treatment, the HIMAC operating costs (water, electricity, lighting, etc.), and the maintenance and management costs for running the facility.

Patients and Treatment Techniques

Patient Characteristics

Until the present, a total of 46 protocols have been established for carbon ion radiotherapy, and phase I/II and II studies have been conducted in an attempt to identify tumor sites suitable for this treatment and to determine optimal dose-fractionations and irradiation methods for treatment of the specific diseases (Table 1).^{11–13} The number of patients has increased year by year, and the facility has meanwhile

Table 1. Dose-Fractionation employed in Carbon ion RT at NIRS.

Site	Dose-Fractionation (GyE/fr/week)	Gy/fr	BED ($\alpha/\beta = 10$)	BED ($\alpha/\beta = 2.5$)	
H&N:	ACC,MM etc	57.6/16/4	3.6	78.3	140.5
	Sarcoma	70.4/16/4	4.4	101.4	194.3
CNS		58.0/20/5	2.9	74.8	125.3
Skull Base		57.6/16/4	3.6	78.3	140.5
NSCLC: (Stage I)	Peripheral type	90.0/18/5	5.0	135.0	270.0
		72.0/9/3	8.0	129.6	302.4
	Hilar type	60.0/4/1	15.0	150.0	420.0
		42.0/1/1day	42.0	–	–
Liver:	HCC	79.5/15/5	5.3	121.6	248.0
		69.6/12/3	5.8	110.0	231.1
		58.0/8/2	7.2	100.1	226.2
		52.8/4/2	13.2	122.5	331.6
		33.6/2/2days	16.8	90.0	259.4
Bone/Soft tissue		70.4/16/4	4.4	101.4	194.3
Prostate		66.0/20/5	3.3	87.8	153.1
Pancreas:	Pre-ope.	30.0/8/2	3.2	41.3	75.0
	Radical	38.4/12/3	3.8	50.7	87.6
Rectum		73.6/16/4	4.6	107.5	209.0

reached a capacity that has permitted nearly 500 patients per annum to be treated in recent years (Fig. 2). The registration of patients totals 2,867 (3,028 lesions) as of August 2006, and the categories of diseases that can be treated under the Advanced Therapy program approved by the government include head and neck cancer, lung cancer, liver cancer, prostate cancer, bone and soft-tissue sarcoma, pelvic recurrences of rectal cancer, skull base tumor, and choroidal melanoma (Fig. 3).

Irradiation Techniques

The initial process from patient referral to the commencement of radiotherapy is summarized as follows.

When the patient is referred to our Institute, the preliminary screening process takes place to determine whether or not this particular patient is eligible for carbon ion therapy

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 prospects of the therapeutic outcome in order to obtain the patient's informed consent. The signed consent form is then submitted to the Ethical Review 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 procedure to ensure the proper administration of carbon ion radiotherapy is the fabrication of immobilization devices for each particular patient. CT

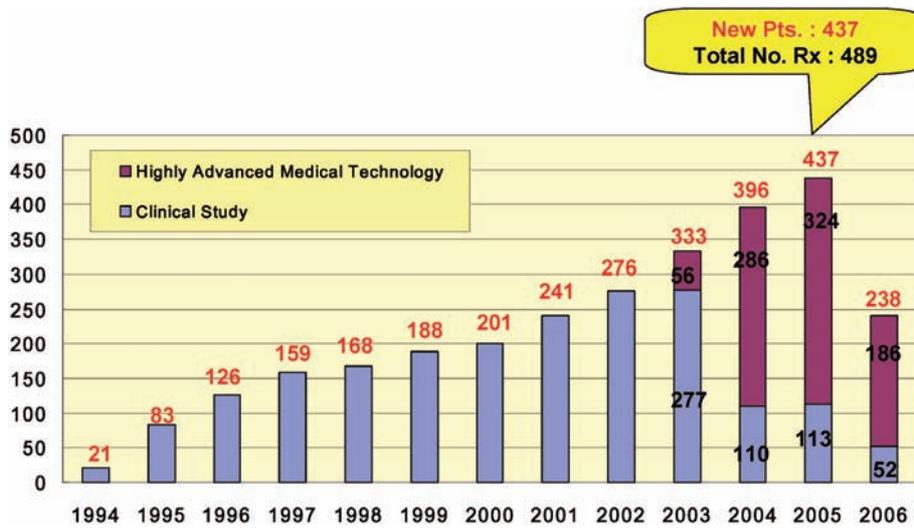


Fig. 2. Number of Patients registered in Carbon Ion Therapy at NIRS (Period: June 1994~August 2006).

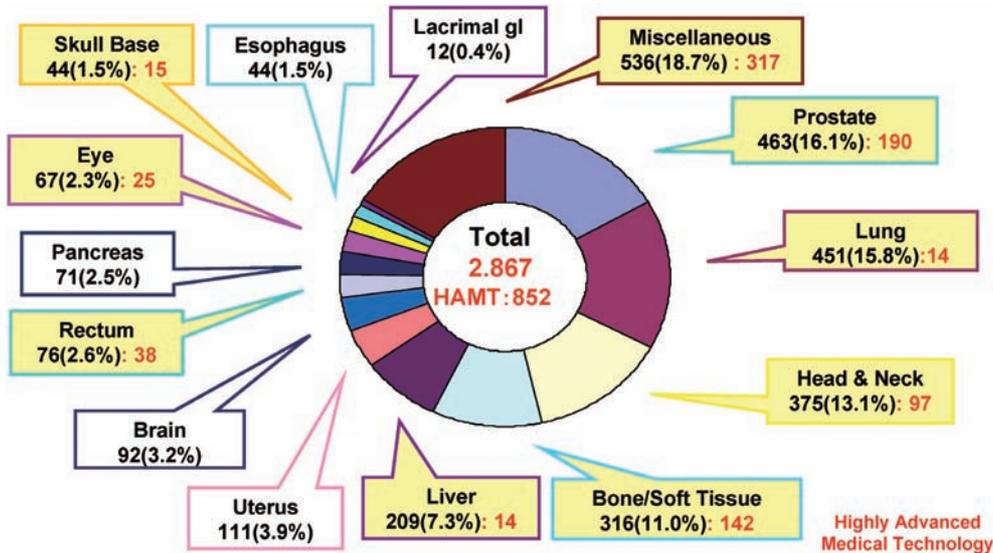


Fig. 3. Number of Patients registered in Carbon Ion Therapy at NIRS (Period: June 1994~August 2006).

scans for treatment planning are then taken with the patient wearing these devices. If the patient requires respiratory-gated irradiation, the respiration synchronizing devices will also be applied at the time of these CT scans.¹⁴⁾ The CT image data obtained in this manner are then transferred to the treatment planning system. At this stage, the irradiation parameters in terms of the number of irradiation portals and irradiation directions are determined in conjunction with the delineation of the target volume. Based on this, the dose distribution is calculated using software called HIPLAN.¹⁵⁾

Once the patient-specific irradiation parameters have been determined, the next step is to design the bolus and collimators for the selective irradiation of the tumor in the body strictly in accordance with these parameters. Based on these preparations, the patient-specific irradiation parameters and dose distribution have now been determined and the calculation results are now presented to an open discussion among radiation oncologists and medical physicists, who examine their appropriateness. In many instances, the outcome of these deliberations will be a review request, and modification of the treatment planning may also be required. Clearly, if such review or restart 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 the particular patient have been determined and the bolus and collimators 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 radiotherapy session and carrying out a mockup rehearsal.

Irradiation Delivery

In carbon ion radiotherapy it is essential 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

their shape has to be designed so that the target volume will be irradiated uniformly within the SOBP. For this purpose, using human salivary gland (HSG) cells, which are the same as parotid cancer cells as a representative of the tumor cells, the dose distribution is determined in such a manner that the HSG cells will be killed uniformly along the SOBP.^{16,17)} The tumor survival rate after irradiation of 30 fractions of 2 Gy each by x-ray is then used to design an 18-fraction schedule in such a manner that the resulting tumor cell survival rate after the irradiation of a single dose is 0.33.

The dose is indicated in GyE, a unit calculated by multiplying the physical carbon dose by the RBE so as to permit a comparison with photon beams: $\text{GyE} = \text{Physical dose} \times \text{RBE}$. It should be pointed out that the RBE of the carbon ion beams used for radiotherapy is 3.0 at the distal part of the SOBP. This value is identical with the RBE of fast neutron beams used for the fast neutron beam radiotherapy previously provided at NIRS.¹⁸⁾

Dose Fractionation

Carbon ion radiotherapy is available on four days a week (Tuesdays through Fridays). The Institute is in principle closed for therapy on weekends and on Mondays. On these days, the accelerator is subjected to maintenance or is used for physical-biological experiments. Recently Monday has become available for therapy once a month.

In dose escalation studies for carbon ion radiotherapy, the same rule of fixing both the total number of fractions and the overall treatment time has been employed, and the total dose, hence the single-fraction dose has been escalated in incremental steps of 5 or 10%. After the recommended dose had thus been established in the phase I/II study, it was then used in the next phase II study. Supposing that a fractionation regimen of 16 fractions given in four weeks had been selected and that the total dose of 57.6 GyE had been increased by 5% to 60.5 GyE, this means that the single-

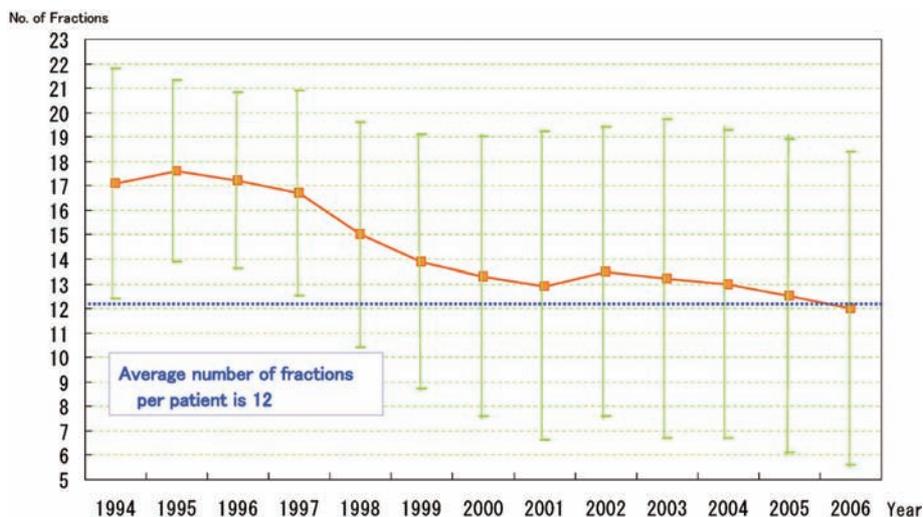


Fig. 4. Average Number of Fractions in Carbon Ion Radiotherapy.

fraction dose had been stepped up from 3.6 GyE to 3.8 GyE, seeing that the irradiation time and fraction number had been fixed. Once the recommended dose has been found from the dose escalation study, it has been employed in phase II studies or HAMT.

As stated earlier, carbon ion beams have a therapeutically favorable biological dose distribution. Utilizing these properties makes it possible to complete the therapy in a short time. Progress in dose escalation has already been made on a scale that permits the radiotherapy course for stage I lung cancer and liver cancer to be completed in 1 and 2 irradiation sessions, respectively. Even for prostate cancer and bone/soft-tissue sarcomas that generally require a relatively prolonged irradiation time, it is possible to accomplish the treatment course with carbon ion beams in about 16 to 20 frac-

tions, approximately half the fraction number required for x-ray and proton beam therapy. At present, the average number of fractions and the treatment time per patient is 12 fractions and 3 weeks, respectively (Fig. 4). The number of registered patients has been steadily increasing year after year and, apart from the fact that the irradiation methods have been firmly established and therapy can be administered without difficulty, this may be accounted for by the significant shortening in the number of fractions and the treatment time per patient.

RESULTS OF CARBON ION RADIOTHERAPY BY TUMOR TYPE

The details of each treatment have been described previ-

Table 2-1. Summary-Results of carbon Ion Radiotherapy at NIRS (Treatment Period: 6.1994~2.2006).

Protocol	Pha-se	Tumors	GyE/frs/wk	No. Pats	3-year Local Control	Overall Survival		Comments
						3-yr	5-yr	
Head&Neck-1+2	I / II	Locally advanced	49~70/16~18/4~6	34	81%	48%	37%	
Head&Neck-3(9602)	II	Locally advanced	57.6/16/4	224	77%	57%	43%	
		- Adenoid cystic ca		64	82%	76%	68%	
		- Adenoca		26	72%	64%	64%	
		- Malignant melanoma		80	88%	49%	30%	
		- Others		54	55%	46%	27%	
Head & Neck-4	I / II	Sarcoma	70.4/16/4	16	100%	56%	56%*	*4-yr survival
Head&Neck-5	II	Malignant melanoma	57.6/16/4	57	82%	42%	35%*	
		- C-ion +Chemotherapy		48	92%	45%	45%*	
Skull base/ cervical spine	I / II	Skull base/cervical spine	48.0~60.8/16/4	40	93%	94%	87%	
		- Chordoma		25	88%	100%	86%	
Lung-1(9303)	I / II	Stage I (Peripheral type)	59.4~95.4/18/6	47	65%	-	42%(61%)*	* Figures in () indicate
Lung-2(9701)	I / II	Stage I (Peripheral type)	72.0~79.2/9/3	34	91%	-	41%(60%)*	cause-specific survival
Lung-3(9802)	II	Stage I (Peripheral type)	72.0/9/3	50	95%	-	50%(76%)*	
Lung-4(0001)	I / II	Stage I (Peripheral type)	52.8~60.0/4/1	79	90%	-	41%(62%)*	
Lung-3+4	-	Stage I (Peripheral type)	4 and 9 fractions	129	93%	-	44%(71%)*	
		- I A (\leq 3 cm)		71	99%	-	56%(88%)*	
		- I B (> 3 cm)		58	85%	-	30%(48%)*	
Lung-5(0201)**	I / II	Stage I (Peripheral type)	28~44 (Single irrad)	116	-	-	-	** On-going dose-
Lung-6(9801)	I / II	Stage I (Central type)	57.6~61.2/9/3	23	91%	-	21%(39%)	escalation study
Lung-7(9903)	I / II	Locally advanced	68~76/16/4	37	88%	-	38%(55%)	
Liver-1	I / II	T2~4 MONO	49.5~79.5/15/5	24	81%	50%	25%	
Liver-2	I / II	T2~4 MONO	48~70/4~12/1~3	82	87%	48%	26%	
Liver-3	II	T2~4 MONO	52.8/4/1	44	95%	58%	35%	* Pats with good liver
Liver-2+3	-	All cases treated with 4 frs	52.8/4/1	61	94%	57%	33%	function:
		- with localized tumor*		21	-	71%	67%	single, 3~5 cm
Liver-4	I / II	T2~4 MONO	/2fr/2days	40	-	-	-	

Table 2-2. Summary-Results of carbon Ion Radiotherapy at NIRS.

Protocol	Pha-se	Tumors	C-ion RT GyE/frs/wk	No. Pats	3-year Local Control	Overall Survival		Comments
						3-yr	5-yr	
								5-yr bNED Survival
Prostate-1	I / II	B2~C	54~72/20/5	35	97%	94%	89%	----91%
Prostate-2	I / II	A2~C	60~66/20/5	61	100%	97%	90%	----78%
Prostate-3	II	T1C~C	66/20/5	333	99%	94%	91%	----87%
Prostate-2+3	Total	A2~C	66/20/5	374	99%	95%	92%	----88%
		– Low risk		68	98%	98%	93%	----87%
		– High risk		306	100%	94%	91%	----89%
		– PSA ≤ 20		216	99%	96%	91%	----89%
		– PSA > 20		158	100%	94%	92%	----88%
Cervix-1	I / II	III~IVa (Sq Cell Ca)	53~72/24/6	30	49%	40%	37%	
Cervix-2+3	I / II	II~IVa (Sq Cell Ca)	64~72/20~24/5	36	69%	52%	43%	
		– Stage III			72%	57%	45%	
		– Stage IVa			63%	38%	38%	
Uterus(Adenoca)	I / II	II~IVa (Adenoca)	62.4~71.2/20/5	39	74%	70%	53%	
Bone/Soft Tissue-1	I / II	Unresectable	53~74/16/4	57	63%	47%	36%	Eligibility criteria include
Bone/Soft Tissue-2	II	Unresectable	70.4/16/4	190	82%	67%	54%	the tumor located in the pelvis
Bone/Soft-1+2	–	Osteosarcoma	70.4/16/4	48	69%	51%	34%	and para-spinal region.
		Chordoma	70.4/16/4	69	98%	91%	80%	
Rectum-1	I/II	Pelvic recurrence	67.2~73.6/16/4	65	82%	65%	55%	
Pancreas:								
Preope C-ion-1	I/II	Resectable All	44.8~48.0/16/4	22	–	23.8% (36.3)*		*2-yr Survival
Preope C-ion-2	I/II	Resectable All	30.0~33.2/8/2	11	–	18.0%(40.0)*		**1-yr Survival
Radical C-ion	I/II	Unresectable All	38.4~48.0/12/3	31	–	44.0%**		Figures in () are for resected pats

ously,¹⁹⁾ and are delineated in the subsequent chapters. A brief summary is seen in Table 2.

Head and Neck Tumors

Carbon ion radiotherapy was first applied to the patients with head and neck tumors. The tumor type primarily treated in the Phase I/II clinical studies consisted of tumors in the nasal cavity and paranasal sinus, mostly with invasion to the skull base. Many of these patients had locally advanced or postoperative recurrent cancers considered difficult to cure with other therapeutic procedures. In the initial phase I/II dose escalation study, a fractionation regimen of 18 fractions/6 weeks was applied, with 17 patients having been treated by this protocol up to February 1996. Beginning in April 1996, the second phase I/II dose escalation study was performed using a shorter fractionation of 16 fractions/4 weeks, where a total of 19 patients were enrolled. Comparison of toxicities and local tumor control in these two studies revealed that there was no significant difference between the two treatment schedules.^{20,21)} Beginning in April 1997, the

third Phase II study employed a total dose of 57.6 GyE in 16 fractions over 4 weeks as was determined in the second dose escalation study. Until the present time, this fractionation regimen has not given rise to any particularly serious toxicities. In the treatment of head and neck tumors involving the skull base and paranasal sinus, preservation of visual acuity is of paramount importance and a clear relationship has been found to exist between visual acuity and radiation dose.²²⁾

The treatment results obtained so far can be summarized by stating that a favorable local control rate of as high as 80 to 90% has been achieved mainly in adenocarcinoma, adenoid cystic carcinoma and malignant melanoma in the nasal cavity and paranasal sinus.²⁰⁾ With regard to the long-term survival of malignant melanoma, however, almost one out of two patients eventually died of distant metastasis, hence a combined regimen of carbon ion radiotherapy and chemotherapy was initiated in order to control or prevent distant metastasis. The decision to embark on this chemoradiotherapy was based on the assessment that while radiotherapy on

its own provided favorable local tumor control, further improvements in long-term survival were needed. It has been found that, for bone/soft-tissue sarcoma arising in the head and neck region, a higher dose is needed for achieving a high tumor control, and a total dose of 70.4 GyE in 16 fractions has been used with, so far, satisfactory results.

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

Stage I lung cancer are divided into two groups according to tumor location: peripheral-type and central-type. This classification is made on an assumption that, as the central-type tumor is located more close to the main bronchus than peripheral-type tumor, the two may have different tolerance to radiation and different fractionation regimens should be investigated for each. The patients eligible for either treatment schedule are those for whom surgery is not indicated or those who refuse surgery.

For the peripheral-type of stage I lung cancer, clinical study is currently in progress using a single-fraction irradiation that would produce a result identical to surgery and may be described as the ultimate type of treatment using carbon ions. To arrive at this goal, the fraction number and treatment time had been reduced in gradual steps from 18 fractions/6 weeks through 9 fractions/3 weeks to 4 fractions/1 week.^{19,23)} The 129 patients treated subsequently using the 9-fraction and 4-fraction regimens have shown the results comparable to those achieved with surgery. There were no serious toxic reactions and the local control rate was more than 90%, with a 5-year overall survival rate of 50.0% for 9 fractions and 41.0% for 4 fractions (corresponding cause-specific survival rate was 76% and 62%, respectively). The long-term results using 9 fractions have been reported by Miyamoto.²⁴⁾ A dose escalation study on the single-fraction treatment was initiated with 28 GyE, and it has meanwhile progressed to the 44 GyE level. This clinical study is due to be concluded in the next 6 months.

For the treatment of the central-type of stage I lung cancer, a larger fraction number than for the peripheral-type has been used. This type of cancer is characterized by the presence of a large number of relatively superficial lesions and has therefore been satisfactorily controlled with a lower dose (57.6 GyE/9 fractions/3 weeks) than is necessary for the peripheral-type tumor. It was also found that, for a central-type tumor forming a bulky lesion, a higher dose than was used for the peripheral-type should be employed, and a new Phase I/II study was initiated on carbon-ion therapy using 12 fractions over 3 weeks for patients with a central type of NSCLC with exophytic bronchial mass development.

Locally Advanced Lung Cancer

For locally advanced lung cancer, preoperative irradiation was initially performed in order to make a pathological assessment of the anti-tumor effect of carbon ions.²⁵⁾ Of five patients, surgery was performed as planned on three. In two

of these patients, malignant cells were not found pathologically. Based on this outcome, the second clinical study was performed for locally advanced lung cancer, and 37 patients were eligible for analysis. The results are comparable to surgery in terms of local control and survival rate.

Hepatocellular Cancer

Clinical studies have been carried out on four protocols. The eligibility criteria for the patients to be enrolled into any of these protocols were that other therapies offered no potential of sufficient efficacy or that other treatments had proven ineffective in local tumor control. In the first phase I/II dose escalation study, 24 patients were treated with a total dose ranging from 49.5 GyE to 79.5 GyE given in fixed 15 fractions and 5 weeks. Both 3-year and 5-year local control rates in this study were 81%.²⁶⁾ In the second phase I/II study, successive dose escalation was implemented from 12 fractions/3 weeks through 8 fractions/2 weeks to 4 fractions/1 week in an attempt to develop a short-course irradiation regimen. It was possible to conduct all of these fractionation regimens with acceptable toxicities. Based on these results, the phase II study using a total dose of 52.8 GyE in 4 fractions over 1 week was conducted. This total dose was the recommended dose determined in the second dose escalation study. The total number of patients treated with four fractions in both the second and third clinical studies was 61, and the results indicated that this was a satisfactory fractionation schedule in terms of both hepatic toxicity and local tumor control. Post-treatment impairment in hepatic function was minimal in these patients and the 5-year local control and 5-year survival rates were recorded as 94% and 33%, respectively.²⁷⁾ More recently, the fourth clinical study using an even shorter irradiation schedule of 2 fractions in 2 days has just been closed, with encouraging results in terms of a favorable local control rate and the absence of any particularly serious toxic reactions. This two-fractionated treatment is now being used under HAMT.

Prostate Cancer

A total of three clinical studies have so far been carried out. The dose fractionation for these studies used fixed fractions of 20 given in 5 weeks. The first study with carbon ion radiotherapy (total dose ranging from 54.0 to 72.0 GyE) combined with hormone therapy was conducted for stage B2-C tumor. The treatment for the second study consisted of carbon ion radiotherapy alone (total dose of 60.0 GyE or 66.0 GyE) for stage A2-B1, and carbon ion radiotherapy (total dose of 66.0 GyE) combined with hormone therapy for stage B2-C. In the first dose escalation study, grade 3 toxicities in the rectum were recorded among patients exposed to the highest total dose of 72.0 GyE.²⁸⁾ As a result, a dose tolerable for the rectum was established and no serious toxic reactions were subsequently encountered in later clinical studies. DVH analysis was also performed to identify the

tolerance dose of the rectum, with the results having yielded a DVH curve that permits the risks of rectal reactions to be predicted. This curve is of immense usefulness and has made it possible to prevent severe reactions in new patients by comparing the DVH curves at the time of treatment planning.

Based on these studies, it was thus possible to establish an irradiation schedule for prostate cancer and to commence the third Phase II clinical study in April 2000. In this study, the patients were divided into high-risk and low-risk groups on the basis of their various pre-treatment factors (PSA, Gleason Score, and TNM classification). The high-risk group received combined carbon radiotherapy and hormone therapy while the low-risk group was treated with carbon ion therapy alone. Therapy was administered at a fixed total dose of 66 GyE in 20 fractions over 5 weeks. The dose was reduced by 5% for patients associated with severe diabetes mellitus. There have been no serious toxic reactions to date, and the survival rate has also been satisfactory.^{29,30)} This dose corresponds to the tolerance dose for both the rectum and the urethra and is at the same time also virtually sufficient to achieve a high local tumor control.³¹⁾

External radiotherapy with x-rays for prostate cancer is generally performed using around 40 fractions in 7–8 weeks at a dose per fraction of 1.8–2.0 Gy. In contrast, carbon ion radiotherapy has been performed with a much shorter fractionation schedule of only 20 fractions in 5 weeks. So far, local recurrence was discovered in only one out of 374 patients who were treated with a fixed total dose of 66GyE. More recently, even a shorter irradiation schedule with 16 fractions in 4 weeks has been employed with encouraging survival and acceptable toxicities.

Bone and Soft-Tissue Sarcomas

As bone and soft-tissue sarcomas are generally considered to be photon-resistant and because of the frequent presence of critical organs in their vicinity, conventional radiotherapy is only applied to limited cases. Advanced tumors originating from the para-spinal region, the pelvis and the retroperitoneum, in particular, are in many cases not suited for surgical resection and have a poor prognosis. Such patients have been almost totally excluded from treatment with conventional radiotherapy. The use of carbon ion beams now offers a favorable prospect of improved local control in view of their superior biological dose distribution.

The patients enrolled in the initial phase I/II dose escalation study were primarily those not suited to surgical resection or were entirely inoperable. This study produced a favorable local control rate of 63%, and it was found, in particular, that chordoma and osteosarcoma in the pelvis are prime candidates for carbon ion radiotherapy.^{32–34)} Some 10% of those patients with lesions close to the skin surface so that it was not possible to avoid irradiation of the skin to high doses were found to develop severe reactions such as

fibrosis or ulceration of the skin and subcutaneous tissues. However, as more experience has been gained and significant improvements in irradiation techniques have been achieved, such severe reactions no longer occur. It has also been established that there is a definite proportional relationship between the total dose and local tumor control. In view of these findings, the recommended dose has been fixed at 70.4 GyE in 16 fractions in 4 weeks.³²⁾ The 5-year local control rate and 5-year overall survival rate for the 48 osteosarcoma patients were 57% and 34% and for the 47 chondrosarcoma patients 62% and 38%, respectively. The 69 chordoma patients (excluding patients with the base of the skull primaries) have a 5-year local control rate of 96% and a 5-year overall survival rate of 80%. A report on the 30 sacral chordoma patients who were observed for a period of two years or longer was published previously.³³⁾

Bone and soft-tissue sarcomas in the trunk are the most typical lesions qualifying for carbon ion radiotherapy. For tumors of the extremities, clinical studies are in progress with a view to developing a treatment that permits the preservation of the extremities.

Rectal Cancer (Postoperative pelvic recurrence)

Although postoperative rectal cancer recurrence in the pelvis has decreased as a result of improvements in surgical techniques, its incidence is still in a range of 10 to 40%.^{35–37)} Many of the patients with local recurrence are not eligible for surgical resection and are frequently referred to radiotherapy. Yet the results of radiotherapy are still far from adequate, with many studies in the literature reporting a 50% survival period of 12 months and a three-year survival rate of around 10%, and the role of radiotherapy is often described as mere pain control.

So far 65 patients have been treated with carbon ion radiotherapy and no particularly serious toxic reactions have been observed. The results in terms of local control and survival rate have been encouraging in comparison with conventional radiotherapy and are comparable to those achieved with surgery. None of 32 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 overall local control rate was 82% at 3 years of follow-up. The median survival time was 38 months (range, 7 to 52 months), and the 3- and 5-year overall survival rates were 65% and 55%, respectively.

Thus, 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.

Uterine Cancer

The mortality of uterine cancer is following a declining trend, and the treatment results have been relatively favorable through the combination of intra-cavitary brachytherapy and external beam radiotherapy. The treatment results of

uterine cancer in advanced stage, however, are at the present still unsatisfactory. This has led to attempts to apply new therapies such as chemoradiotherapy. Carbon ion radiotherapy is now being applied mainly to locally advanced lesions in an attempt to achieve some new breakthrough in therapeutic results that have seen little or no progress.³⁸⁾

The treatment results of carbon ion radiotherapy for squamous cell carcinoma of the uterine cervix have shown that serious toxic reactions occurred in the gastrointestinal tract in our early period after the inception of clinical studies, with some patients requiring surgical intervention. In later clinical studies, however, improvements in safety were achieved as a result of more effective irradiation techniques, and as dose escalation proceeded, the local control rate was also improved.³⁹⁾ Although dose escalation studies are still in progress, carbon ion radiotherapy is considered effective for the treatment of stage III and stage IVa cervical squamous cell carcinoma.⁴⁰⁾

Treatment of uterine adenocarcinoma has been targeted primarily at non-resectable cervical cancer. In 39 patients with locally advanced adenocarcinoma, no patient developed severe acute toxicity and no patient developed major late complications except for one patient with a rectovaginal fistula. Local tumor control was dependent upon the total dose and was 74% at 3-years after the treatment. The 3- and 5-year overall survival rates for all patients were 70% and 53%, respectively. Although the number of patients is small, these results suggest that carbon ion radiotherapy provides favorable local tumor control and overall survival with acceptable rates of late complications in locally advanced cervical adenocarcinoma.

Pancreas Cancer

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

In carbon ion therapy, attempts have been made to improve local efficacy first, and to establish therapeutic strategies involving concomitant use of chemotherapy for the future. In the first clinical study on preoperative carbon ion irradiation with 16 fractions in 4 weeks, 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. The overall actuarial local control rates at the primary tumor bed were 100% at 1 year and 87% at 2 years of

follow-up. One local failure was observed in the residual pancreas at 18 months after pancreaticoduodenectomy. The 2-year overall survival rates were 24% for all patients and 36% for the resected group, respectively. These results have led to the second study of preoperative irradiation with 8 fractions in 2 weeks.

In the dose escalation study on carbon ion radiotherapy alone for locally advanced tumors, 31 patients with clinical stages IVa or IVb and without distant metastasis were enrolled. Carbon ion radiotherapy was given once daily, 4 days a week, for fixed 12 fractions in 3 weeks. The dose was set at 38.4 GyE and escalated to 48.0 GyE at 5% increments. All patients completed the scheduled treatment course and toxicities were all within acceptable levels. The overall local control rate and survival rate at one-year were 81% and 44%, respectively.

These results suggest the potential benefit of carbon ion radiotherapy for pancreatic carcinoma compared to conventional photon radiotherapy. The study will soon be extended to carbon ion radiotherapy with concomitant use of gemcitabine.

Esophageal Cancer

Advanced cancer of the esophagus had been treated with carbon ion radiotherapy in the past. Currently, it is again targeted and as the first step a protocol for preoperative irradiation has been carried out. Its purpose is to improve the survival rate by using a short-course carbon irradiation, with plans for the future use of combined treatment modalities involving the concomitant use of other therapies such as chemotherapy. In patients receiving preoperative carbon ion irradiation delivered in 8 fractions in 2 weeks, histological confirmation of the resected specimen has been studied.

Eye tumors

Lacrimal Gland Cancer

Malignant epithelial tumors originating in the lacrimal gland have a low incidence in Japan. Surgery offers poor results because of difficulty in the total eradication of tumors. This calls for therapeutic modalities permitting high local control with retention of the eyeball and vision. For this purpose, carbon ion radiotherapy has been employed with a 12-fractions/3 weeks irradiation schedule. Until the present, 12 patients have been treated with a total dose of 48 GyE in 5 and 52.8 GyE in 7 patients. It has been shown that determination of the target volume is vital for the prevention of marginal recurrence.

Choroidal Melanoma

This disease is relatively rare in Japan, inflicting about 30~40 patients a year. In western countries it has been treated with proton radiotherapy, which offers superior results in terms of both eyeball and vision retention. The aspects by which carbon ion radiotherapy provided at NIRS differs from proton radiotherapy are, in particular, that carbon ion

radiotherapy uses CT scanning in treatment planning, that it is primarily applied to large tumors that are generally excluded from proton radiotherapy, and that irradiation is performed from two portals to ensure maximum possible prevention of cataract and neo-vascular glaucoma.^{41,42)} At present, this disease qualifies for treatment under the HAMT.

Skull Base and Cervical Spine Tumor

Skull base tumors, involving mainly chordoma and chondrosarcoma, are in most cases difficult to resect surgically and are generally resistant to conventional radiation. The therapeutic results had therefore been rather poor. While improvements have been achieved with proton radiotherapy, it has been pointed out that in the case of chordoma there are still many cases with recurrence even after five years of treatment.⁴³⁾ Carbon ion radiotherapy holds a promising potential for improving these poor long-term results. Until the present, 40 patients have been treated, with the local effectiveness being favorable without serious toxic reactions.

Brain Tumor

Malignant glioma including anaplastic astrocytoma and glioblastoma is most difficult to control, similar to pancreatic cancer. Until the present, two clinical studies have been conducted. In the first study, x-ray irradiation was performed first at 50 GyE/25 fractions/5 weeks and ACNU was concomitantly administered in the first week and the fourth or fifth week after the commencement of irradiation. Following this, exclusive carbon ion radiotherapy was applied at 8 fractions/2 weeks with dose escalation at five dose levels. The results have demonstrated that the local control and survival rates are improved with dose escalation, confirming the validity of carbon ion radiotherapy. No late toxicities of grade 3 or worse were observed in regions beyond the target volume. While improvement has thus been achieved in the local control with carbon ion radiotherapy, the long-term survival rate is still unsatisfactory and further improvements are needed. At present, a second clinical study with carbon ion irradiation alone is in progress, but more cases still have to be compiled as this study has only just begun.

DISCUSSION

The promising aspect of carbon ion radiotherapy for cancer therapy lies in the superior biological dose distribution that makes the carbon ion beam the best-balanced particle beams available. Thus, comparison of the ratio of the RBE in the peak region against the RBE in the plateau region shows that, of all heavy ion species, carbon ion beams have the most favorable value. This is the most important reason for NIRS choosing the carbon ion beams. Carbon ion radiotherapy also makes use of the property of forming a spread-out Bragg peak that is unique to ion beams. This permits irradiation of a high dose even when there are critical organs

in the vicinity of the target lesion. Furthermore, the carbon ion beam has the RBE two or three times that of photon beams and therefore has the potential of providing a high local effect in particular for the treatment of sarcomas and adenocarcinomas. Recent basic research also suggests the possibility that particle beams may be effective in preventing cancer metastasis, the potential that may become a third promising aspect of carbon ion radiotherapy in the treatment of cancer.⁴⁴⁾

NIRS had been also providing radiotherapy with fast neutron and proton beams, but only carbon ion radiotherapy has been approved under the Advanced Therapy program for the first time. At our Center, an Examining Committee for Advanced Therapy has been established to ensure the effective provision of Advanced Therapy. In addition, an Eligibility Investigation Committee for Carbon Ion Radiotherapy is in place to make medical assessments as to the eligibility of patients for treatment. The Guidelines for Advanced Therapy contain detailed rules on the execution of Advanced Therapy, and for certain diseases the present therapeutic results may not be satisfactory. Thus, for example, further efforts are needed to improve therapeutic outcomes for certain extremely intractable cancers such as brain tumor and pancreas cancer. As a result, clinical studies are and will be continued for such tumors. In this manner, NIRS will provide carbon ion radiotherapy as part of its mission as a medical institution by offering Advanced Therapy in parallel with clinical studies.

Carbon ion radiotherapy at NIRS has made significant progress, with a total of more than 3,000 patients registered until the end of 2006. Our experience to date can be summed up by characterizing carbon ion radiotherapy as follows: 1) By location, it is effective for the head and neck, 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 adenocarcinoma, adenoid cystic carcinoma, hepatocellular carcinoma and sarcomas including malignant melanoma and bone/soft-tissue sarcoma.

The unique advantages of carbon ion radiotherapy in terms of its favorable physical and biological dose distribution as described earlier can be utilized to provide a short-course hypofractionated regimen that is effective in treatment of many types of tumors. For lung and liver cancer, in particular, an ultra-short irradiation schedule capable of being completed in only 1 or 2 fractions is available. Even for prostate and uterine cancers a relatively short-course irradiation of 20 fractions in 5 weeks, and for head and neck as well as bone/soft-tissue sarcomas treatment with only 16 fractions in 4 weeks are possible. These fractionation regimens are much shorter than those used for the most sophisticated photon radiotherapy techniques such as IMRT and 3-D conformal radiotherapy. For certain tumors such as malignant melanoma of the head and neck and pancreas tumors, it is important to develop methods for preventing distant

metastasis so as to improve the survival rate still further. In this context, combined carbon ion radiotherapy with anti-cancer drugs has been initiated.

For intractable tumors such as malignant glioma, pancreas cancer, uterine cancer and esophageal cancer, it will be necessary to further improve therapeutic outcomes. To this end, clinical studies are continued. In terms of toxicities (side-effects), significant progress has been made, as the adverse effects 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.

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