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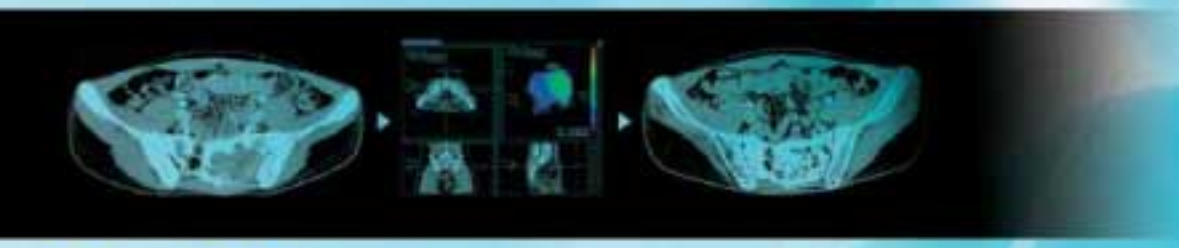

Special issue

Progress to Date in Carbon Ion Radiotherapy

-Present Status and Outlook-

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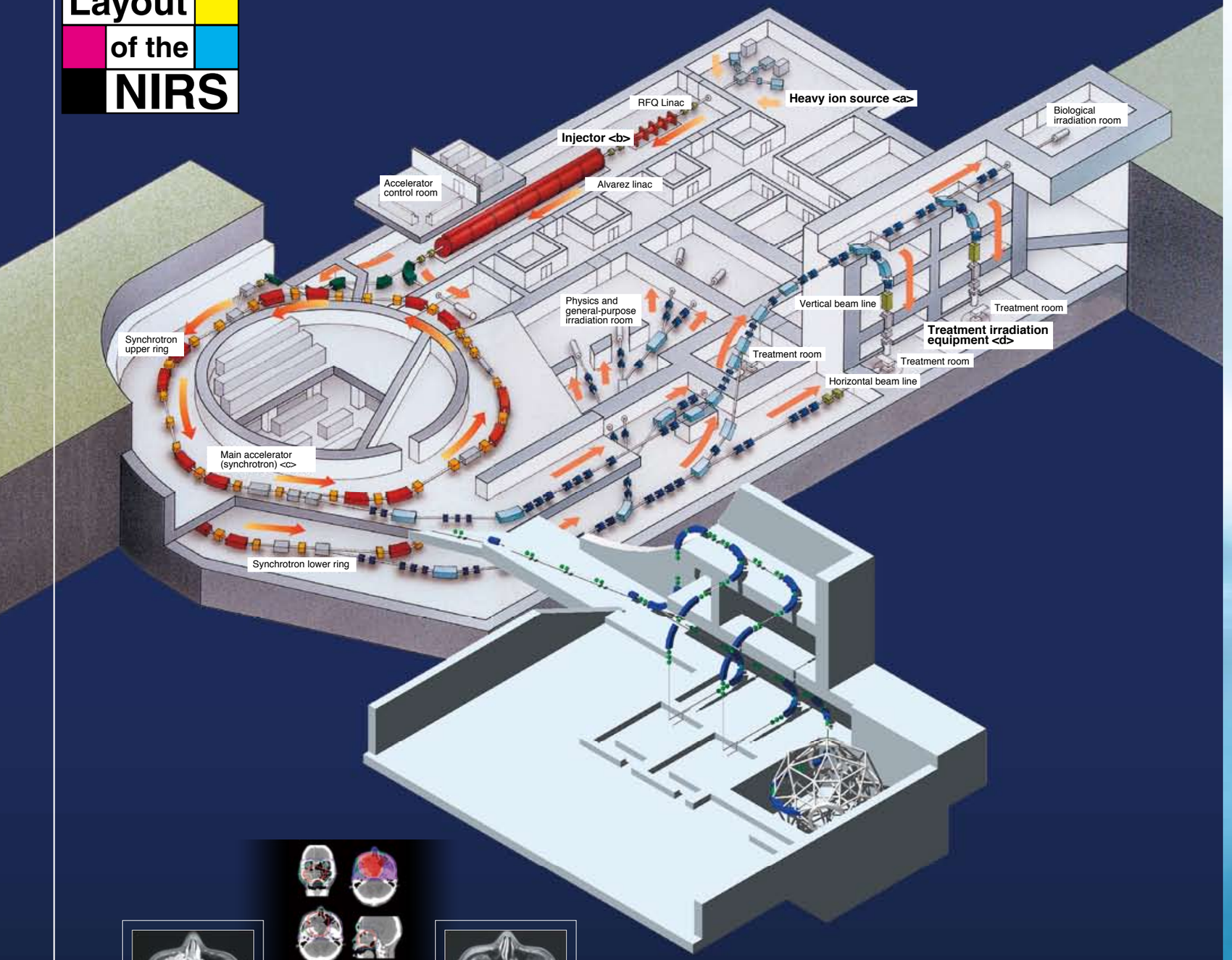
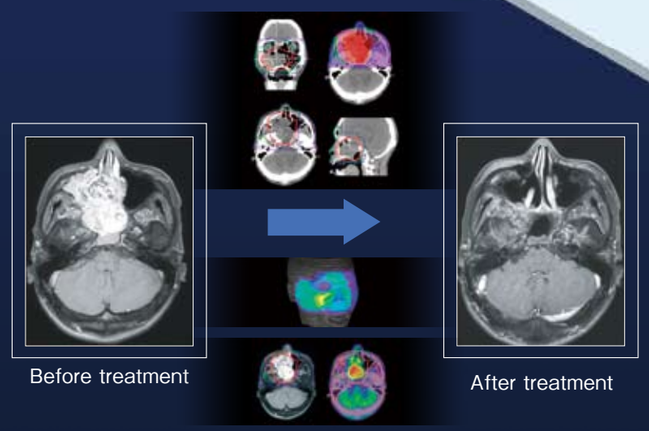
Layout of the NIRS





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Contents

Special Issue

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Progress to Date in Carbon Ion Radiotherapy
—Present Status and Outlook

Hirohiko Tsujii
Director of the Research Center for Charged Particle Therapy

Introduction

On June 21, 1994, the National Institute of Radiological Sciences (NIRS) started heavy ion radiotherapy using carbon ion beams generated by the Heavy Ion Medical Accelerator in Chiba (HIMAC). Since then, clinical studies to develop safe and secure irradiation technologies and optimized dose fractionation for various diseases have been conducted, and the radiotherapy was approved as a "highly advanced medical technology (HAMT)" in October 2003. Recently, the name of HAMT has been changed to an "advanced medicine," which is an intermediate step to being approved as a treatment under the national health insurance system in Japan. At NIRS, more than 3,100 patients have been treated, and the clinical efficacy of carbon ion radiotherapy has been demonstrated for many diseases.

HIMAC was constructed as part of the "Comprehensive 10-Year Strategy for Cancer Control" that started in 1984. It was the first heavy ion medical accelerator in the world and has been operated as a multipurpose facility open to international and domestic researchers for biological, physical, and accelerator engineering studies as well as cancer treatment. The number of research studies conducted with HIMAC during the past 10 years is 120 or more per year, and the number of users is 500 to 600 with related research performance increasing greatly in quality and quantity.

HIMAC has thus accomplished great results in the fields of clinical applications and basic studies. Before HIMAC was constructed, the Japanese medical use of particle beams had always relied on foreign accelerators. Since the construction of HIMAC, Japan has become a world leader in the field of medical use of heavy ion beams, which could be an admirable feat.

A carbon ion beam used in cancer radiotherapy is characterized by better dose distribution and higher biological effect than that in conventional radiation. The carbon ion beam is therefore expected to be effective against intractable, photon-resistant cancers, and to greatly reduce the treatment period compared with photon or proton radiotherapy. The results of our previous and ongoing clinical studies, those from advanced medicine, and a number of irradiation technologies developed suggest that this is true.

However, the data collected to date may not be sufficient enough to fully prove the efficacy of carbon ion radiotherapy, and more clinical data are needed. It is a duty of NIRS to provide these data. This special issue introduces the past, present, and future plan of charged particle radiotherapy at NIRS.

《I》 The past, present, and future of heavy ion radiotherapy studies

1. Clinical results of Carbon Ion Radiotherapy at NIRS

Durectir of the Research Center for Charged Particle Therapy
Hirohiko Tsujii, Tadashi Kamada, Junetsu Mizoe, Masayuki Baba, Hiroshi Tsuji, Hirotoshi Kato, Shingo Kato, Shigeru Yamada, Shigeo Yasuda, Takeshi Yanagi, Reiko Imai, Hiroyuki Kato, Ryusuke Hara, Naotaka Yamamoto, Norio Sugane, Azusa Hasegawa, Ryo Takagi, Mio Nakajima, Tomoaki Tamaki, Hiroki Kiyohara, Hiroshi Imada, Takuma Nomiya, Hiroki Bessho, Takeshi Onda, Susumu Kandatsu, Kyosan Yoshikawa, Riwa Kishimoto, and Hidefumi Ezawa

1. Features of heavy charged particle beams in cancer radiotherapy

The particle beams being currently used for treatment in humans are proton and carbon beams. Other particle beams that have been used for humans include negative pi meson beams, helium beams, neon beams, silicon beams, and argon beams (Fig. I-1-1). Each of these beams has specific characteristics, but only proton and carbon beams are now used for treatment[1]. In general, particles heavier than the electron that are accelerated to a high speed are called heavy charged particle beams[2], but the names of particle beams are not always internationally unified and require special attention. In some EU countries, charged particle radiotherapy is collectively called hadron radiotherapy or, with particle masses around or less than the carbon nucleus mass, light ion radiotherapy. In Japan, the term heavy ion beam often refers to carbon ion beam unless otherwise specified.

Carbon beams and proton beams have the common feature of producing maximum ionization immediately before coming to rest to form a Bragg peak. This feature is very advantageous in cancer radiotherapy and allows a high dose to be given safely even if there are critical organs close to or in contact with the lesion.

The biological effect of ionizing radiation is caused by damage to DNA depending on the ionization density produced along the radiation track. Average energy transferred per unit length of the track is called a linear energy transfer (LET) and becomes larger as the mass of the particle increases or the particle goes deeper (Fig. I-1-2). Since LET in the peak of a carbon beam is larger than that of a photon beam and a proton beam, it has biological features beneficial to cancer radiotherapy: relative biological effectiveness (RBE) being 2 to 3 times larger, less recovery from radiation damage in the target volume, less dependence of the radiation effect on oxygen concentration in the tissue, and a small difference in radiological sensitivity through the cell cycle. The RBE of particle beams becomes larger as the mass of the particle increases. When the ratios of the RBE in the plateau area to that in the peak area are compared, the carbon beam has the largest value among various ion beams,[3] suggesting it is the best balanced particle beam.[4] This is the main reason we have selected the carbon beam for cancer radiotherapy at NIRS.

In summary, the carbon beam among heavy charged particle beams has not only improved physical dose distribution like the proton beam but also has a larger RBE as the ion beam travels deeper inside the body, demonstrating better biological dose distribution than other ion beams. It is therefore expected to have smaller side effects on the surrounding normal tissues and higher

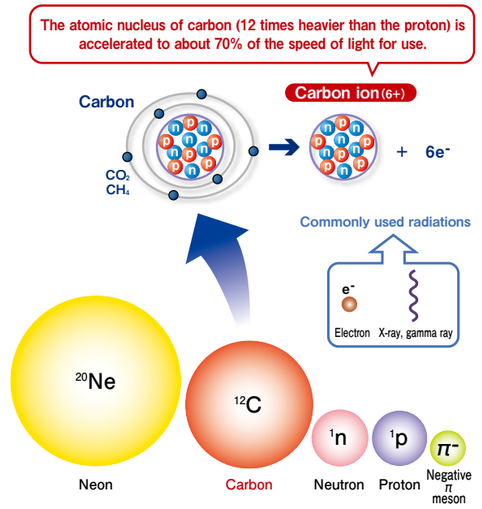


Fig. I-1-1 Types of radiation

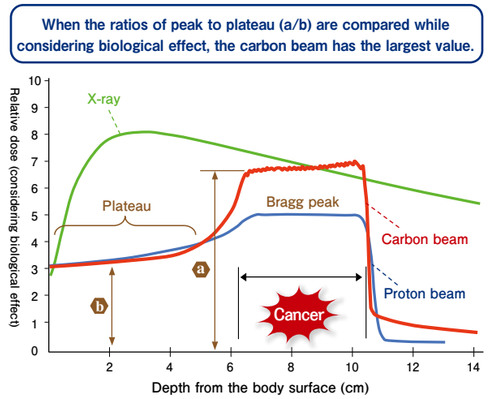


Fig. I-1-2 Dose distribution of various radiations considering biological effect

biological effects on intractable cancers resistant to X-rays and proton beams.

Additionally, the carbon beam has a therapeutic advantage for its short course of radiotherapy.1, [5] This will be described later.

2. Organization for conducting clinical studies with the carbon ion beam and the advanced medicine

Since its inception, NIRS has endeavored continuously to perform carbon ion radiotherapy ethically and scientifically under a number of committees headed by the carbon ion radiotherapy network committee. Figure I-1-3 shows the organization for performing carbon ion radiotherapy. All protocols for clinical studies were designed by tumor-specific subcommittees and the Planning Committee, reviewed by the Ethical Review Board, and finally approved by the Network Committee, the topmost committee. The appropriateness of continuing individual clinical studies was reviewed by the Evaluation Committee, and the results were submitted to the Network Committee whose meetings were always held publicly. A total of 100 or more meetings on clinical aspects have been held each year.

All the carbon ion radiotherapy had been performed as a prospective clinical study. In October 2003, the technology was approved as a form of "highly advanced medical technology" under the name of "heavy ion radiotherapy for solid tumors." This is a medical technology which is performed in "a medical facility specifically approved by the government" in order to coordinate advanced medical technology and general health insurance treatment in response to the advent of new medical technologies and diversified need for medical treatment. As a patient-funded option, it has become possible to collect extra charges for highly advanced medical technology from patients in addition to the ordinary medical costs (co-payment of health insurance). Costs relating to the highly advanced medical technology were calculated considering costs for the construction of HIMAC, personnel, consumption supplies, operation of accelerators (such as utilities expenses), and maintenance.

In October 2006, the Health Insurance Law was partially amended, in which the "specified medical treatment coverage system" was abolished and reconstituted into a new framework as "evaluation medical treatment" and "elective medical treatment." Evaluation medical treatment is new modalities which are not yet confirmed for its medical effectiveness and are not currently covered by health insurance, but will be covered by health insurance in the future. Elective medical treatment is treatment that is not assumed to be covered by health insurance but can be only chosen by patients themselves if desired. This new system expands the range of options by allowing patients to receive health insurance benefits for the basic part of the entire medical cost and to pay all extra charges that are not included in the evaluation medical treatment or elective medical treatment. In other words, it has been made possible to combine advanced medical technologies not covered by health insurance with health insurance if these meet certain conditions. In the new system, treatment modalities are classified into highly advanced medical technology and advanced medicine, allowing the combined use of health insurance and patient-funded treatment. In summary, highly advanced medical technology was subject to strict approval requirements, for example, its ability to be used only in "specially approved medical facilities" such as university hospitals. However, the reorganization of the medical treatment system not covered by health insurance has allowed the highly advanced medical technology to be performed in any medical institution if it meets the approval requirements for "advanced medicine."

Although the approval of carbon ion radiotherapy as an "advanced medicine" has allowed the radiotherapy to be integrated into general medical treatment, the results obtained for some diseases have not yet been sufficient. For example, further improvement of treatment for such tumors as brain tumors and pancreatic cancers are strongly required. NIRS therefore continues clinical studies on carbon ion radiotherapy for these tumors as well as performing advanced medicine.

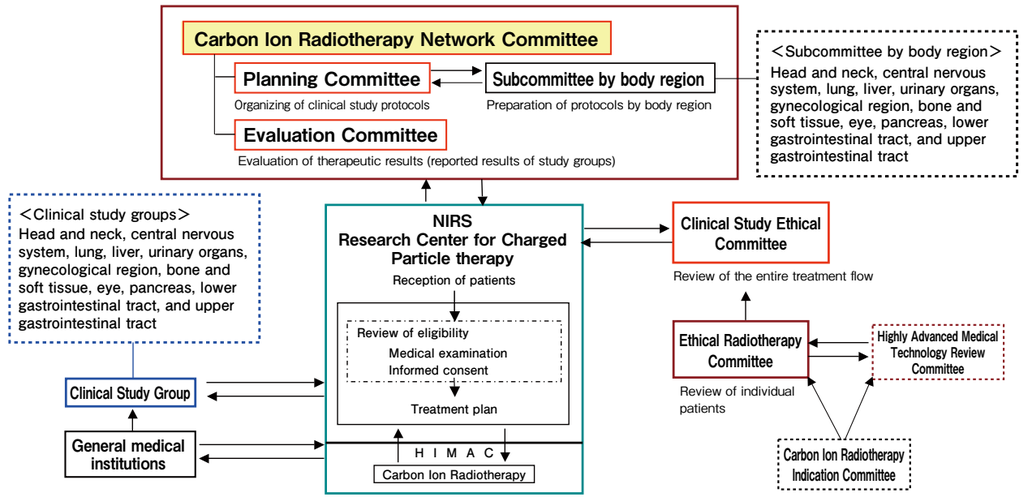


Fig. I-1-3 System for performing carbon ion radiotherapy in NIRS

Table I-1-1 List of protocols for carbon ion radiotherapy

Protocol name	Number	Phase		Enrollment period (scheduled)
Head and neck tumors	(9301)	Ⅰ/Ⅱ	18 fractions /6weeks	Completed (June 1994-February 1996)
Head and neck tumors II	(9504)	Ⅰ/Ⅱ	16 fractions /4weeks	Completed (April 1996-February 1997)
Head and neck tumors III	(9602)	Ⅱ	16 fractions/ 4weeks	(April 1997-) (November 2003-) Advanced medicine
Head and neck tumors IV (bone and soft tissue)	(0006)	Ⅰ/Ⅱ	16 fractions /4weeks	(April 2001-)
Head and neck tumors V (malignant melanoma)	(0007)	Ⅱ	16 fractions /4weeks	(April 2001-) (November 2003-) Advanced medicine
T3/T4 tongue cancers	(9304)	Ⅰ/Ⅱ	Heavy ion + surgery, 16 fractions /4 weeks	Completed (September 1994-February 1995)
Central nervous system tumors	(9302)	Ⅰ/Ⅱ	X-ray + heavy ion, 25 fractions /5 weeks + 8 fractions / 2 weeks	Completed (September 1994-February 2002)
Central nervous system tumors II	(0101)	Ⅰ/Ⅱ	Heavy ion, 20 fractions /5 weeks	(April 2002-)
Non-small-cell lung cancers	(9303)	Ⅰ/Ⅱ	Lung field type + locally advanced cancer, 18 fractions /6 weeks	Completed (October 1994-August 1998)
Non-small-cell lung cancers II	(9701)	Ⅰ/Ⅱ	Lung field type + locally advanced cancer, 9 fractions/ 3 weeks	Completed (September 1997-February 1999)
Non-small-cell lung cancers III	(9801)	Ⅰ/Ⅱ	Hilar proximate type, 9 fractions /3 weeks	Shifted to 2 in September 2005
Non-small-cell lung cancers IV	(9802)	Ⅱ	Lung field peripheral type, 9 fractions /3 weeks	Completed (April 1999-February 2001)
Non-small-cell lung cancers V	(9903)	Ⅰ/Ⅱ	Locally advanced cancer, 16 fractions /4 weeks	(April 2000-February 2003) (November 2003-) Advanced medicine
Non-small-cell lung cancers VI	(0001)	Ⅰ/Ⅱ	Lung field peripheral type, 4 fractions /1 week	Completed (October 2000-February 2003)
Non-small-cell lung cancers VII	(0005)	Ⅰ/Ⅱ	Hilar and mediastinal lymph node metastasis, 12 fractions /3 weeks	(April 2001-)
Non-small-cell lung cancers VIII	(0201)	Ⅰ/Ⅱ	Lung field type, 1 fraction	(April 2003-)
Non-small-cell lung cancers IX	(0503)	Ⅰ/Ⅱ	12 fractions /3 weeks	(April 2006-)
Hepatocellular carcinoma	(9401)	Ⅰ/Ⅱ	15 fractions / 5 weeks	Completed (April 1995-February 1997)
Hepatocellular carcinoma II	(9603)	Ⅰ/Ⅱ	12 fractions3 weeks→8 fractions/2 weeks→4 fractions / 1 week	Completed (April 1997-February 2001)
Hepatocellular carcinoma III	(0004)	Ⅱ	4 fractions /1 week	Completed (April 2001-February 2003)
Hepatocellular carcinoma IV	(0202)	Ⅰ/Ⅱ	2 fractions /2 days	Completed (April 2003-September 2005) (September 2005-) Advanced medicine
Metastatic liver cancers	(0506)	Ⅰ/Ⅱ	1 fraction	(April 2006-)
Prostate cancers	(9402)	Ⅰ/Ⅱ	Carbon ion + hormone	Completed (April 1995-October 1997)
Prostate cancers II	(9703)	Ⅰ/Ⅱ	Carbon ion alone and carbon ion + hormone	Completed (October 1997-February 2000)
Prostate cancers III	(9904)	Ⅱ	20 fractions/5 weeks	Shifted to 2 in September 2005
Cervical cancers	(9403)	Ⅰ/Ⅱ	Equal fractionation	Completed (April 1995-November 1997)
Cervical cancers II	(9702)	Ⅰ/Ⅱ	Increasing dose only in the primary region	Completed (October 1997-February 2000)
Cervical cancers III	(9902)	Ⅰ/Ⅱ	20 fractions /5 weeks	Completed (April 2000-February 2006)
Uterine cancers IV	(0508)	Ⅰ/Ⅱ	20 fractions /5 weeks	(April 2006-)
Uterine adenocarcinoma	(9704)	Ⅰ/Ⅱ	12 fractions/3 weeks + boost, 8 fractions /2 weeks	(April 1998-)
Comprehensive study I	(9404)	Ⅰ/Ⅱ	Those to which treatment by the fractionation regimen confirmed safety is applicable	(April 1995-) (November 2003-)Advanced medicine
Comprehensive study II	(9404)	Ⅰ/Ⅱ	Basic studies on protocol development	(April 1995-)
Bone and soft tissue tumors	(9501)	Ⅰ/Ⅱ	16 fractions /4 weeks	Completed (April 1996-February 2000)
Bone and soft tissue tumors II	(9901)	Ⅱ	16 fractions /4 weeks	Shifted to 2 in September 2005
Esophageal cancers (preoperative)	(9502)	Ⅰ/Ⅱ	20 fractions /5 weeks	Completed (April 1996-February 1999)
Esophageal cancers (radical)	(9503)	Ⅰ/Ⅱ	24 fractions /6 weeks	Completed (April 1996-February 1999)
Esophageal cancers (preoperative)	(9905)	Ⅰ/Ⅱ	Resection is not indicated, 12 fractions /3 weeks	Completed (April 2000-February 2001)
Esophageal cancers (preoperative short-term)	(0301)	Ⅰ/Ⅱ	8 fractions /2 weeks	(July 2004-)
Rectal cancers (postoperative recurrence)	(0003)	Ⅰ/Ⅱ	16 fractions /4 weeks	(April 2001-) (April 2004-) Advanced medicine
Skull base tumors	(9601)	Ⅰ/Ⅱ	Separated from the comprehensive study, 16 fractions /4 weeks	(October 1996-) (April 2004-) Advanced medicine
Pancreatic cancers I (preoperative)	(9906)	Ⅰ/Ⅱ	16 fractions /4 weeks	Completed (April 2000-February 2003)
Pancreatic cancers II (preoperative)	(0203)	Ⅰ/Ⅱ	8 fractions /2 weeks	(April 2003-)
Pancreatic cancers III	(0204)	Ⅰ/Ⅱ	Locally advanced, 12 fractions /3 weeks	(April 2003-)
Pancreatic cancers IV (combined with chemoradiotherapy)	(0513)	Ⅰ/Ⅱ	Locally advanced, 12 fractions /3 weeks	Start was postponed
Eye tumors II	(0002)	Ⅰ/Ⅱ	Heavy ion	Shifted to 2 in September 2005
Eye tumors	(P9601)	Ⅱ	Proton beam radiotherapy	Completed (September 1996-July 2003)
Lacrimal gland I	(0102)	Ⅰ/Ⅱ	12 fractions /3 weeks	(April 2002-)

Table I-1-2 Number of patients enrolled on carbon ion radiotherapy in NIRS (enrollment period, June 1994 to February 27, 2007)

Body Region	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Clinical	2003 Advanced	2004 Clinical	2004 Advanced	2005 Clinical	2005 Advanced	2006 Clinical	2006 Advanced	Subtotal Clinical	Subtotal Advanced	Total	
Head and neck	9	10	19	31	22	38	29	39	40	26	9	9	36	4	31	7	49	283	125	408	12.8%
Central nervous system	6	8	10	6	9	7	15	10	6	5		3		4		4		93	0	93	2.9%
Skull base				6	4	2	2	4	8	3			8		5		4	29	17	46	1.4%
Lung	6	11	28	18	29	36	47	51	57	46	4	47	8	44	1	35	4	455	17	472	14.9%
Liver		12	13	19	25	17	22	28	18	22		14		4	10	3	5	197	15	212	6.7%
Prostate		9	18	10	30	30	31	44	47	54	23		62		73		84	273	242	515	16.2%
Gynecological region (uterine)		9	13	11	10	11	13	5	10	7		8		10		8		115	0	115	3.6%
Bone and soft tissue			9	13	19	18	25	23	32	35	8		57		52		58	174	175	349	11.0%
Gastrointestinal tract (esophagus)			1	16	4		2					9		9		6		47	0	47	1.5%
Pancreas							3	7	12	18		11		13		20		84	0	84	2.6%
Rectum (postoperative)								10	13	15			18		11		21	38	50	88	2.8%
Eye (malignant melanoma)								8	16	18			13		4		13	42	30	72	2.3%
Lacrimal gland									5	3				4				12	0	12	0.4%
Comprehensive		24	15	29	16	29	12	12	12	25	12	9	84	21	137	55	173	259	406	665	20.9%
Subtotal										277	56	110	286	113	324	138	411	2101	1077	3178	100.0%
Total	21	83	126	159	168	188	201	241	276	333		396		437		549		3178			

Clinical, Clinical study; Advanced, Advanced medicine

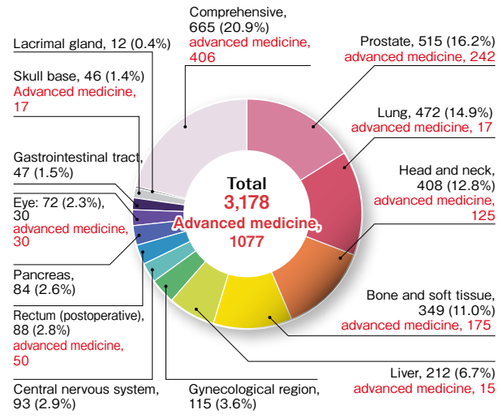


Fig. I-1-4 Number of patients enrolled for carbon ion radiotherapy (June 1994 to February 27, 2007)

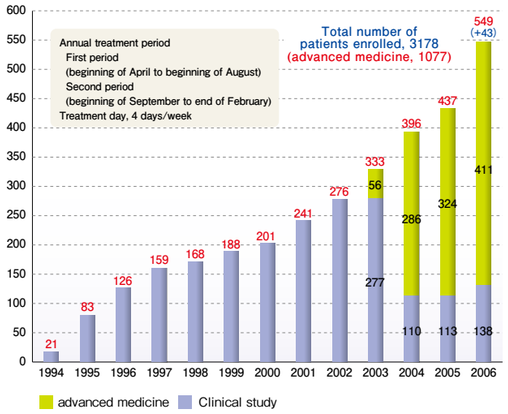


Fig. I-1-5 Number of patients enrolled for carbon ion radiotherapy (June 1994 to February 27, 2007)

3. Results of carbon ion radiotherapy

3-1 Outline of the protocols

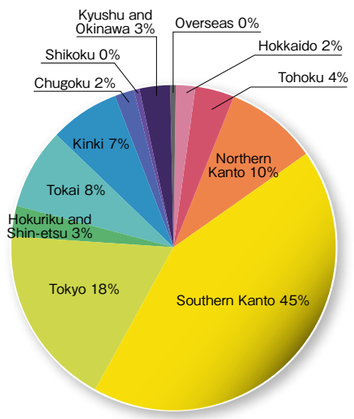
Carbon ion radiotherapy started on June 21, 1994 at NIRS and has mainly focused on the group of diseases that are difficult to cure using conventional radiotherapy, and among them are head and neck tumor, brain tumor, lung cancer, hepatocellular carcinoma, prostate cancer, uterine cervix cancer, bone and soft tissue tumor, and esophageal cancer. Table I-1-1 shows a list of protocols designed to date.

The total number of patients enrolled by February 2007 was 3,178 (3,362 lesions) where various types of tumors were treated (Table I-1-2 and Fig. I-1-4). In the phase I/II studies to confirm the safety of carbon ion radiotherapy and to obtain a clue to an anti-tumor effect, the number of fractions and treatment period were fixed for each disease and the total dose was gradually increased by 5 to 10%. When the recommended dose was determined in the phase I/II studies, they were incorporated into the phase II studies. As shown in Fig. I-1-5, the number of the patients enrolled has increased year after year. This increase occurred as the treatment regimen became established and could be smoothly executed, thereby the number of fractions and treatment period per patient was greatly reduced.

Since carbon ion radiotherapy has been focused on such tumors that are hard to cure with conventional radiotherapy, patients come from all areas of Japan, although the Kanto area, where NIRS is located, predominates (Fig. I-1-6). The Kanto area is the place

Table I-1-3 Fractionation regimen and biological effective dose (BED) in major regions of the body

Body Region		Fractionation regimen (GyE/fractions/week)	Dose/fraction (GyE)	BED(α/β=10)	BED(α/β=2.5)
Head and neck: adenocarcinoma,melanoma, and sarcoma		57.6/16/4	3.6	78.3	140.5
		70.4/16/4	4.4	101.4	194.3
Brain		58.0/20/5	2.9	74.8	125.3
Skull base		57.6/16/4	3.6	78.3	140.5
Lung (stage I): Peripheral type		90.0/18/5	5.0	135.0	270.0
		72.0/9/3	8.0	129.6	302.4
		60.0/4/1	15.0	150.0	420.0
		28.0/1/1day	28.0	-	-
		44.0/1/1day	44.0	-	-
	Hilar nontumorigenic type	54.0/9/3	6.0	86.4	183.6
	Hilar nontumorigenic type	68.4/12/3	5.7	107.4	224.4
Liver:	Hepatocellular carcinoma	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	100.0	226.2
		52.8/4/2	13.2	122.5	331.6
		38.8/2/2day	19.4	114.1	339.9
Bone and soft tissue		70.4/16/4	4.4	101.4	194.3
Prostate		66.0/20/5	3.3	87.8	153.1
Pancreas:	Preoperative	33.6/8/2	4.2	47.7	90.1
	Radical	50.4/12/3	4.2	71.6	135.1
Rectum (postoperative pelvic recurrence)		73.6/16/4	4.6	107.5	209.0



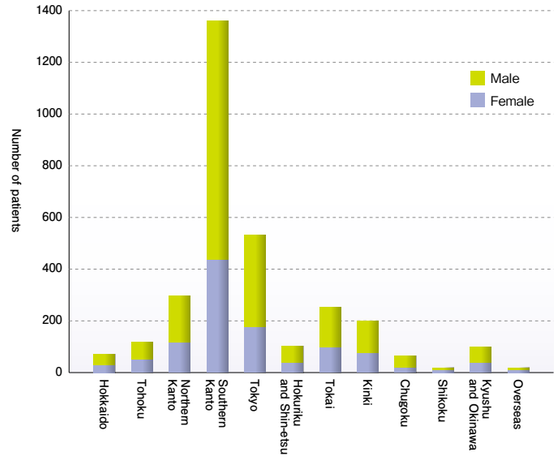


Fig. I-1-6 Regional distribution of patients' place of residence

of residence for 72% of patients (Southern Kanto 44.8%, Tokyo 17.6%, and Northern Kanto 9.5%), followed by Tokai 7.6%, Kinki 6.6%, Tohoku 3.6%, Hokuriku and Shin-etsu 3.2%, and others 7.0%. The predominance of patients from areas around Chiba is probably associated with access to information on carbon ion radiotherapy and the availability of transportation for cancer patients, many of whom are elderly. The referring facilities were mostly university hospitals and cancer centers in the surrounding area. These factors should be kept in mind when considering the location of treatment facilities.

Since a carbon ion beam has the therapeutically advantageous feature of a higher RBE at deeper sites from the surface of the body, treatment can be completed in a shorter period. For stage I lung and liver cancers, for example, treatment can be completed in one or two irradiation fractions. For prostate cancer and bone/soft tissue tumors, it is completed in 16 to 20 fractions, which is about half the number of fractions employed in X-ray and proton beam radiotherapy (Table I-1-3). The average number of treatment fractions per patient is now 13 and the treatment period are about 3 weeks in NIRS.

3-2 Toxicities

About half of the patients enrolled were treated in the phase I/II studies (dose escalation studies) aimed at determining the optimal dose fractionation for each tumor site. The most appropriate recommended dose in terms of safety and anti-tumor effect was determined by increasing the total dose by 5 to 10% increments with the treatment fractions and treatment time being fixed. In dose escalation studies, better local control is expected with larger total doses but adverse reactions become larger. It is ideal

Table I-1-4 Results of carbon ion radiotherapy at NIRS (treatment period, June 1994 to February 2007)

Protocol	Phase	Target	Irradiation regimen (fractions/week)	Number of patients	3-year local control	Survival		Remarks
						3-year	5-year	
Head and neck-1+2	Ⅰ/Ⅱ	Locally advanced cancer	49～70/16～18/4～6	34	81%	48%	37%	
Head and neck-3 (9602)	Ⅱ	Locally advanced cancer	57.6/16/4	284	73%	57%	43%	
		- Adenoid cystic carcinoma		85	89%	77%	67%	
		- Adenocarcinoma		37	81%	63%	47%	
Head and neck-4		- Malignant melanoma		93	86%	58%	44%	*4-year survival
Head and neck-5	Ⅰ/Ⅱ	- Others		69	50%	42%	33%	
		Sarcoma	70.4/16/4	23	100%	61%	41%*	
		Malignant melanoma	57.6/16/4	63	76%	56%	49%*	
		- Carbon beam and chemoradiotherapy		54	83%	59%	59%*	
Skull base/ paracervical spine	Ⅰ/Ⅱ	Skull base/paracervical spine	48.0～60.8/16/4	42	93%	94%	88%	
		- Chordoma		25	89%	100%	88%	
Lung-1 (9303)	Ⅰ/Ⅱ	Stage I (lung field type)	59.4～95.4/18/6	47	65%	64%	41% (61%) *	
Lung-2 (9701)	Ⅰ/Ⅱ	Stage I (lung field type)	72.0～79.2/9/3	34	91%	55%	40% (58%) *	
Lung-3 (9802)	Ⅱ	Stage I (lung field type)	72.0/9/3	50	95%	66%	50% (76%) *	
Lung-4 (0001)	Ⅰ/Ⅱ	Stage I (lung field type)	52.8～60.0/4/1	79	90%	62%	36% (69%) *	( ) *Survival rate due to primary disease
Lung-3+4	-	Stage I (lung field type)	4- and 9-session fractionated irradiation	129	93%	64%	43% (73%) *	* *Dose escalation is being studied
		- ⅠA (≦3cm)		71	99%	78%	55% (88%) *	
		- ⅠB (＞3cm)		58	85%	47%	29% (51%) *	
Lung-5 (0201)**	Ⅰ/Ⅱ	Stage I (lung field type)	28 to 44 (single fractionrradiation)	120	70%	49%	-	
Lung-6 (9801)	Ⅰ/Ⅱ	Stage I (hilar type)	57.6～61.2/9/3	23	91%	64%	31% (68%)	
Lung-7 (9903)	Ⅰ/Ⅱ	Locally advanced cancer	68～76/16/4	37	88%	38%	38% (56%)	
Liver-1	Ⅰ/Ⅱ	T2～4 MONO	49.5～79.5/15/5	24 (24)	81%	50%	25%	
Liver-2	Ⅰ/Ⅱ	T2～4 MONO	48～69.6/4～12/1～3	82 (86)	87%	48%	26%	
Liver-3	Ⅱ	T2～4 MONO	52.8/4/1	44 (47)	96%	58%	35%	( ) Number of lesions
Liver-2+3	-	52.8Gy/4fraction treatment	52.8/4/1	61 (69)	94%	57%	34%	
		52.8Gy/4fraction treatment (single 3 to 5 cm)	52.8/4/1	20 (22)	91%	75%	70%	
Liver-4	Ⅰ/Ⅱ	T2～4 MONO	32.0～38.8/2 fr/2 days	36 (36)	84%	77%	-	
Prostate-1	Ⅰ/Ⅱ	B2～C	54～72/20/5	35	97%	94%	89%	5-year disease-free survival 91%
Prostate-2	Ⅰ/Ⅱ	A2～C	60～66/20/5	61	100%	97%	90%	5-year disease-free survival 78%
Prostate-3	Ⅱ	T1C～C	66/20/5	365	99%	94%	92%	5-year disease-free survival 90%
Prostate-2+3	All cases	A2～C	66/20/5	406	99%	94%	92%	5-year disease-free survival 88%
		- Low risk		75	98%	96%	96%	5-year disease-free survival 88%
		- Medium risk		77	100%	95%	95%	5-year disease-free survival 98%
		- High risk		254	100%	94%	91%	5-year disease-free survival 86%
		- PSA ＜20		235	99%	95%	93%	5-year disease-free survival 90%
		- PSA ＞20		171	100%	94%	92%	5-year disease-free survival 86%
Uterus-1	Ⅰ/Ⅱ	Ⅲ to Ⅳa (squamous cell carcinoma)	53～72/24/6	30	49%	40%	37%	
Uterus-2+3	Ⅰ/Ⅱ	Ⅱ to Ⅳa (squamous cell carcinoma)	64～72/20～24/5	36	72%	52%	45%	
		- Stage Ⅲ			74%	56%	46%	
		- Stage Ⅳa			63%	38%	38%	
Uterine adenocarcinoma	Ⅰ/Ⅱ	Ⅱ to Ⅳa (adenocarcinoma)	62.4～71.2/20/5	39	68%	68%	54%	
Bone and soft tissue-1	Ⅰ/Ⅱ	Unresectable	52.8～73.6/16/4	57	63%	47%	36%	
Bone and soft tissue-2	Ⅱ	Unresectable	70.4～73.6/16/4	246	84%	68%	49%	Including the pelvis and paracervical spine
Bone and soft tissue-1+2	-	Osteosarcoma	52.8～73.6/16/4	50	57%	42%	25%	
		Chordoma	52.8～73.6/16/4	79	96%	91%	81%	
Rectum-1	Ⅰ/Ⅱ	Postoperative pelvic recurrence	67.2～73.6/16/4	71	86%	64%	42%	
Pancreas: preoperative-1	Ⅰ/Ⅱ	Resectable All	44.8～48.0/16/4	22	-	23.8% (36.3) *		* 2-year survival ** 1-year survival ( ) resection case
preoperative-2	Ⅰ/Ⅱ	Resectable All	30.0～33.2/8/2	11	-	20.0% (40.0) *		
locally advanced	Ⅰ/Ⅱ	Unresectable All	38.4～48.0/12/3	36	-	43.5%**		
Esophagus: preoperative	Ⅰ/Ⅱ	Locally advanced cancer T3-T4	48.0～54.0/20/5	7	-	14%		
alone	Ⅰ/Ⅱ	Unresectable T3-T4	52.8～72.0/24/6	14	-	7%*		* 2-year survival
preoperative short-term	Ⅰ/Ⅱ	Resectable T1b-T3	28.8～35.2/8/2	24	-	78%*		

Table I-1-5 Carbon ion radiotherapy for non-small-cell lung cancer (State I)

Protocol	9303 (Phase Ⅰ/Ⅱ)	9701 (Phase Ⅰ/Ⅱ)	9801 (Phase Ⅰ/Ⅱ)	9802 (Phase Ⅱ)	0001 (Phase Ⅰ/Ⅱ)	0201 (Phase Ⅰ/Ⅱ)
Period	10/'94～9/'97	9/'97～2/'99	4/'98～	4/'99～12/'00	12/'00	4/'03～
Type of tumor	All body regions*	Peripheral type	Central type	Peripheral type	Peripheral type	Peripheral type
Total dose (GyE)	59.4～95.4	68.4～79.2	57.6～64.8	72	54 or 60	28～44
Number of fractions /week	18/6 weeks	9/3 weeks	9/3 weeks	9/3 weeks	4/1week	1
Number of patients (number of lesions)	47 (48)	34 (34)	15 (15)	50 (51)	79 (80)	120 (120)
Adenocarcinoma/ squamous cell carcinoma/large-cell cancer	26/22/0	18/15/1	13/2/0	32/19/0	53/24/2	75/42/1

* Including the peripheral and central types

to terminate the dose escalation immediately before development of severe adverse reactions. This was possible in many protocol studies, but the patients irradiated with high doses for prostate, uterine cervix, or esophageal cancers in the earliest phase I/II studies developed severe gastrointestinal side effects. After the cause of these side effects was examined in detail, a safe dose was determined, and irradiation techniques were improved, no similar side effects were observed.

3-3 Local control and survival

More than 50 protocols for various tumors have been designed and used in clinical studies. Table I-1-4 summarizes the treatment results of each tumor sites.

1) Head and neck tumors

Carbon ion radiotherapy was first started for head and neck tumors in 1994. Most patients had locally advanced lesions or postoperative recurrences with little cure expected from other therapies. Tumors in the nasal cavity and accessory nasal sinus infiltrating into the skull base were most common tumors treated with carbon ions. In the first phase I/II study, a fractionation regimen with 18 fractions over 6 weeks was employed and a total of 17 patients were enrolled by February 1996. Thereafter, 19 patients were enrolled in the second phase I/II study using a fractionation regimen of 16 fractions over 4 weeks. Comparison of the results in these two studies showed no difference in terms of side effects and local control.[6] Since April 1997, phase II studies using 57.6 to 64.0GyE in 16 fractions over 4 weeks, the optimal dose determined in the second study, have been conducted, and no severe side effects have been observed to date. Regarding the preservation of visual acuity, which was one of the most important purposes, there was no clear relationship between the total dose and visual acuity but the target volume irradiated was an important factor. [7]

With respect to anti-tumor effects, the local control has been favorable, being 80 to 90% in adenocarcinomas, adenoid cystic carcinomas, and malignant melanomas. Because the cause of death in most malignant melanoma patients was distant metastasis, the combination of carbon ion radiotherapy and chemoradiotherapy was started. It was expected that from this treatment higher local control and prolonged survival would be obtained as a result of better tumor control and prevention of distant metastasis.

For the treatment of bone and soft tissue sarcomas in the head and neck region, it was found necessary to increase the total dose to further improve the local control. Thereby, a total dose of 70.4GyE in 16 fractions is now employed with expected improvement of local control.

2) Skull base tumors

A skull base tumor is a term applied to the tumor that develops in the base of the skull, primarily including chordoma and chondrosarcoma. Because the tumors frequently develop in the vicinity of the brain stem, optic nerve, and large vessels, surgical resection is not usually indicated. While the advent of proton radiotherapy has improved the treatment results, it has become clear that the recurrence of chordomas 5 years or more after treatment is not rare.[8] In this respect, carbon ion radiotherapy has the potential to improve the survival in a long-term observation. [9]

The most common types of tumors treated by carbon ions at NIRS are chordomas and meningiomas. As the dose was increased in dose escalation studies, improvement of tumor control was observed but no severe adverse reactions developed. Local control was achieved in all but two patients treated with lower dose, one with chordoma and the other with meningioma. The fractionation regimen of 60.8GyE/16 fractions/4 weeks yielded the best local control with acceptable morbidity.

3) Lung cancer (non-small-cell lung cancer)

The non-small-cell lung cancers were divided according to the location of the tumor into the peripheral-type and central-type. It was thought necessary to change the fractionation regimen depending on the tumor type since the tolerance of the surrounding normal tissue would be different between the two.

Clinical studies have been conducted to establish the short-course radiotherapy regimen for stage I (T1-2/N0/M0), peripheral-type

cancer. Treatment was started with the use of 18 fractions/6 weeks, the same as that for head and neck tumors, and then the number of fractions and treatment time were carefully reduced (Table I-1-5). Adverse reactions in the lung increased as the dose increased, and there was a clear relationship between the total dose and the local tumor control.[10] The respiration-gated irradiation method, a technique synchronizing with the respiratory movement of target organs, was used. The irradiation from 3- to 4-field (directions) was found to be less toxic than that through 1- to 2-field (directions).

We conducted a clinical study to develop a short-course, hypofractionated radiotherapy. The treatment regimens of 9 fractions/3 weeks and 4 fractions/1 week were evaluated, in which the severe toxicity were small and a local control rate of >90% was obtained.[11] When the survival rate was compared with surgical results based on 7,408 cases included in lung cancer registration survey in Japan in 1994 and a joint study of the Japan Lung Cancer Society and the Japanese Association for Chest Surgery, the 5-year survival rate was 71.5% for stage IA and 50.1% for stage IB cancers in surgery cases, while 54.7% for stage IA and 46.1% for stage IB cancers in carbon ion radiotherapy, showing a tendency for survival to be lower for stage IA cases treated with carbon ion radiotherapy. However, the 3-year survival rate was 81.3% for stage IA after surgery and 75.6% in carbon ion radiotherapy, with no marked difference between the two in survival. Considering that the average age of the patients receiving carbon ion radiotherapy was about 75 years, which was about 10 years older than the average age of 65 years in the operated patients, the results of carbon ion radiotherapy for stage I lung cancer may be almost comparable to the surgical results.

The phase I/II dose escalation study was performed for peripheral-type lung cancer using a single fraction. The total dose started at 28.0GyE and increased to 44.0GyE, but so far no serious adverse events have been observed. Single fraction irradiation is the ultimate regimen utilizing the features of a carbon ion beam. We intend to adopt this regimen as an advanced medicine at the earliest possible time.

Clinical studies have also been conducted on carbon ion radiotherapy for locally advanced lung cancers and the hilar type cancers, and case studies are being accumulated. The locally advanced lung cancers included Pancoast tumors and mediastinal type tumors in stages II to IIIA. The overall local control rate was 92.7%, and the cause-specific survival rate at 46 months was 52.7%.

In summary, short course irradiation (9 fractions /3 weeks, 4 fractions/1 week) was confirmed as a safe treatment for the peripheral-type stage I lung cancer in patients for whom surgery was not indicated or who refused surgery. Results where the antitumor effect of the radiotherapy was comparable to, or better than, that of surgery was obtained. The clinical study on the single fraction treatment, where the irradiation is accomplished within one hour, will be terminated soon, and the technique will shift to advanced medicine after the recommended dose is established.

4) Hepatocellular carcinoma

Between April 1995 and August 2005, clinical studies with four protocols were conducted and 197 patients were treated. Since September 2005, an irradiation regimen of 2 fractions/2 days or 4 fractions/4 days has been used as the advanced medicine.

All the clinical studies included patients for whom other therapies were not expected to provide sufficient effects or were not indicated. In the first phase I/II study, 24 patients were treated with irradiation in 15 fractions/5 weeks and the safety and efficacy were confirmed. The 3- and 5-year local control rates were both 81%.[12] In the second phase I/II study, the dose was escalated using increasingly shorter irradiation time of 12 fractions/3 weeks, 8 fractions/2 weeks, and 4 fractions/1 week for the purpose of developing a short course irradiation method. All of the fractionation regimens were confirmed to be safe.[13]

Based on these results, a phase II study (third protocol) to examine the efficacy of treatment with 52.8GyE/4 fractions/1 week was conducted in 47 patients, and there were no or only minimal decreases in liver function in 90% of the patients after the tre-atment. The 3- and 5-year local control rates were both 96%, and the 3- and 5-year cumulative crude survival rates were 58% and 35%, respectively. The 3- and 5-year cumulative crude survival rates in 27 fresh cases were 63% and 40%, respectively, indicating an excellent fractionation regimen in terms of safety and efficacy.[14] In 17 patients with a tumor diameter of more than 3cm and the maximal tumor diameter of 5cm or less in which percutaneous local treatment such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) was difficult, the 3- and 5-year local control rates were both 92% and the 3- and 5-year cumulative crude survival rates were 77% and 65%, respectively. In 11 fresh cases with a tumor diameter of 3 to 5cm, the 3- and 5-year cumulative crude survival rates were 82% and 73%, respectively, which were better than the 3- and 5-year survival rates of 73% and 56% in patients with similar sized tumors (2 to 5cm) receiving liver resection.[15]

Finally, a phase I/II study with the fourth protocol (very short course irradiation of 2 fractions/2 days) was conducted from April 2003 to August 2005, and no severe side effects were observed.[16] This fractionation regimen has been now been adopted as the advanced medicine.

Among the patients treated in the clinical studies were 50 who were fresh cases with a follow-up period of 2 years or longer and were treated with the recommended or larger doses, corresponding to BED (α/β = 10) > 105GyE. In these 50 patients, the 3- and 5-year local control rates were both 92% and the 3- and 5-year cumulative crude survival rates were 63% and 38%, respectively (Table I-1-6). In 24 patients with a tumor diameter of 3 to 5cm, the 3- and 5-year local control rates were both 88%, and the 3- and 5-year cum-ulative crude survival rates were 72% and 66%, respectively. These values are comparable to or even better than the 3- and 5-year survival rates of 73% and 56% in patients with a tumor diameter of 2 to 5cm receiving liver resection.[15]

When the side effects after carbon ion radiotherapy were analyzed, there were few limitations due to liver dysfunction or tumor diameter, and more than 90% of patients were almost free of symptoms during and after the radiotherapy. Patients with cancers with no contact between the tumor and the gastrointestinal tract, moderate or higher liver function, and a tumor diameter of 10cm or less are considered to be good candidates for carbon ion radiotherapy.

5) Prostate cancer

Three clinical studies were completed by October 2003 and since then the treatment has been continued as an advanced medicine. The total number of patients reached is 600 by February 2007. Of these, the number of patients who were treated with 63 or 66 GyE/20 fractions/5 weeks and had an observation period of 6 months or more after treatment was 406.

After the early dose escalation study was terminated, 66GyE/20 fractions/5 weeks has been used as the standard irradiation regimen. Since January 2005, the dose has been reduced to 63GyE/20 fractions/5 weeks to further decrease the incidence of adverse reactions. We have been also conducting treatment with 57.6GyE/16 fractions/4 weeks in parallel with the standard regimen in order to reduce the treatment period. In the near future, we will apply this fractionation regimen to all patients. Patients were classified into two groups, high and low risk groups, by factors before treatment including PSA, Gleason score, and TNM classification to determine the need for combination with endocrine treatment. The high risk group was treated with carbon ion radiotherapy in combination with endocrine therapy and the low risk group was treated with carbon ion radiotherapy alone.[17-19] Since September

Table I-1-6 Charged particle radiotherapy for hepatocellular carcinoma. Study with BED (α/β = 10).

April 1995 to August 2005, number of patients treated in clinical studies: 197
Date of data analysis: January 31, 2007
BED (α/β = 10) > 105 corresponds to the recommended dose or higher in each protocol.

I. Study in 90 patients treated first and followed for 2 years or more

BED (α/β =10)	Number of patients	Local control rate (%)*		Cumulative survival rate (%)*	
		3-year	5-year	3-year	5-year
>105	50	92	92	63	38
<105	40	78	78	60	39

* n.p

II. Study in 43 patients with a tumor diameter of 3 to 5 cm in whom percutaneous local treatment (RFA or PAI) was not indicated, among those treated first and followed for 2 years or more

BED (α/β =10)	Number of patients	Local control rate (%)*		Cumulative survival rate (%)**	
		3-year	5-year	3-year	5-year
>105	24	88	88	72	66
<105	19	70	70	53	38

* n.p,** p=0.06

Table I-1-7 Side effects of carbon ion radiotherapy for prostate cancer

Fractionation regimen	Number of patients	Rectum			Lower urinary tract		
		G0~1	G2	G3	G0~1	G2	G3
5-week 20-fraction regimen							
All patients (54-72 GyE)	461	443	13	5	424	30	7
(%)		(96.1)	(2.8)	(1.1)	(92.0)	(6.5)	(1.5)
All patients after the therapeutic method was established	406	400	6	0	383	23	0
(%)		(98.5)	(1.5)	(0)	(94.3)	(5.7)	(0)
66.0GyE	296	290	6	0	274	22	0
(%)		(98.0)	(2.0)	(0)	(92.6)	(7.4)	(0)
63.0GyE	110	110	0	0	109	1	0
(%)		(100)	(0)	(0)	(99.1)	(0.9)	(0)
4-week 16-fraction regimen							
57.6GyE	74	74	0	0	74	0	0
(%)		(100)	(0)	(0)	(100)	(0)	(0)

2005, patients considered not to require long-term hormone therapy were separated from the high risk group as a medium risk group and the period of the hormone therapy was reduced to 6 months.

The incidence of adverse reactions of Grade 3 or more in the rectum or lower urinary tract (bladder/urethra) in all patients was 1.5%, but no reactions of Grade 3 or more have been observed in any patients after the optimal irradiation dose was established. The incidence of adverse reactions of Grade 2 in the current technique is as low as 1.5% in the rectum and 5.7% in the lower urinary tract and has recently tended to decrease since the total dose was reduced to 63GyE (Table I-1-7). Treatment with 57.6GyE/16 fractions has produced no reactions of degree 2 in 74 patients observed for 6 months or more and this regimen is considered to be comparable to or safer than the treatment with 63GyE/20 fractions.

For the 406 patients observed for 6 months or more, the 5-year survival rate was 91.6%, the cause-specific survival rate was 98.5%, the 5-year local control rate was 99.1%, and the biochemical non-recurrence rate was 88.5%. Analysis of prognostic factors using the biochemical non-recurrence rate as an endpoint revealed that the clinical stage (T-stage) and the Gleason score determined by the same pathologist were significant prognostic factors. A comparison of the biochemical non-recurrence rate in patients with a PSA level of 20 ng/mL or higher before treatment with those receiving other radiotherapies showed a markedly higher non-recurrence rate in those receiving carbon ion radiotherapy (Table I-1-8). The high non-recurrence rate should be also associated with the effects of our sound use of combination hormone therapy, but a comparison with clinical studies in Europe and North America combining hormone therapy and X-ray radiotherapy showed that the survival rate in our results was 10 to 15% higher, confirming that the high local effect of carbon ion radiotherapy led to good treatment results.

Following treatment with 57.6GyE/16 fractions, only 1 out of 74 patients had biochemical recurrence and none has died, although the observation period is still short. This treatment is expected to produce results comparable to or better than 20-fraction 5-week irradiation in terms of the anti-tumor effect with lower risk of adverse reactions and gives great hope for future long-term results.

6) Bone and soft tissue tumors

Bone and soft tissue tumors are diseases for which multidisciplinary treatment based on surgical resection has achieved the most favorable results over the past 20 years. Recently, treatment with brachytherapy as well as external beam radiotherapy has also been used and has played an important role in preserving extremities. However, these tumors are generally radio-resistant and the effect of radiation is not sufficient for patients in whom it is difficult to secure the surgical margin and residual tumor is clearly observed or resection is not indicated. Carbon ion radiotherapy, which shows higher biological effects and dose concentration than conventional radiotherapy, is expected to be effective against such radio-resistant bone and soft tissue tumors.

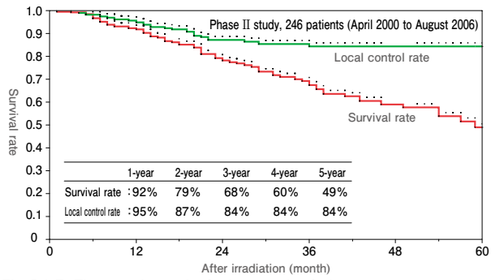


Fig. I-1-7 Therapeutic results for bone and soft tissue tumors

Table I-1-8 A comparison with other radiotherapies

Name of institution	Photon beam			Proton beam	Carbon beam
Therapeutic method	MDACC	FCCC	Cleveland	LLUMC	NIRS
Dose/period	General treatment 66-78 Gy/7-8 weeks	3D layer stacking ≥76Gy/8 weeks	Intensity modulated 70Gy/6 weeks	75CGE/9 weeks	63-66GyE/5 weeks
Delayed adverse reaction					
Number of patients	189	232	100	901	406
Rectum≥G2	14.8%	11.0%	10.0%	3.5%	1.5%
Lower urinary tract ≥G2	8.5%	7.0%	12.0%	5.4%	5.7%
Biochemical non-recurrence rate (PSA before treatment ≥ 20 ng/mL)					
Number of patients	197	232	100	133	171
5-year rate	51%	26~63%	70%	45%	86%

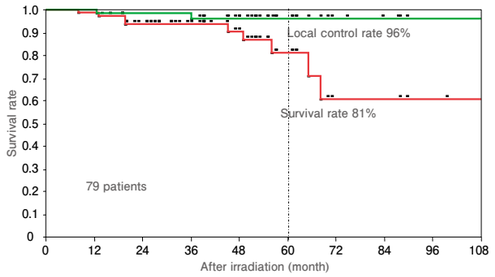


Fig. I-1-8 Therapeutic results for chordomas

Carbon ion radiotherapy for bone and soft tissue tumors was started in 1996 as a phase I/II clinical study (dose escalation study) for those in whom surgical resection was not indicated, then shifted to a phase II clinical study (fixed dose) and is now performed as an advanced medicine. The number of patients with bone and soft tissue tumors enrolled by February 2007 was 345, and the number of patients with bone and soft tissue tumors has recently reached about 100 per year.

The first phase I/II clinical study enrolled 59 patients. The total dose started at 52.8GyE/16 fractions/4 weeks and was increased to 73.6GyE. The local control rate improved as the dose increased but some patients in the group given the largest dose developed severe skin and soft tissue reactions.[20]

The phase II study started in April 2000 and enrolled 246 patients by August 2006. The 3- and 5-year local control rates were both 84% and the 3- and 5-year survival rates were 68% and 49%, respectively (Fig. I-1-7). Skin and soft tissue toxicities, as severe side effects, developed at an incidence of about 3%, but recently, as a result of decreased skin doses, almost no side effect has been observed. In 50 patients with osteosarcomas in the pelvis or spine and whose resection was difficult, the 5-year survival rate was 25%. In 79 patients with chordomas other than those that developed in the skull base, the 5-year local control rate was 96% and the 5-year survival rate was 81% (Fig. I-1-8). Chordomas of the sacral bone was reported in Clinical Cancer Research, 2004 and Lancet Oncology, and appeared in the Year Book of Oncology, 2006.[21,22]

Bone and soft tissue tumors are considered one of the best indications for carbon ion radiotherapy. Although long-term observation should be further continued, carbon ion radiotherapy may replace surgical resection in elderly patients and in patients whose function will be greatly reduced if resected, as well as providing a treatment for patients in whom resection is not indicated.

7) Rectal cancer (postoperative pelvic recurrence)

Due to improved operative techniques and procedures and pre- and post-operative treatment, the local pelvic recurrence rate for rectal cancer has recently decreased but is still as high as 5 to 20%. Surgical resection is the first choice of treatment for recu-rrent lesions, but many of them are unresectable. However, if the recurrent lesion is resectable, the 5-year survival rate after resection of pelvic recurrences is relatively favorable at around 30%.[23] In other words, if the local recurrent lesions can be sec-urely controlled, a favorable prognosis may be expected, but the prognosis with radiotherapy alone is not good and many reports describe a 50% survival period of 12 months and a 3-year survival rate of around 10%.[24]

Carbon ion radiotherapy for postoperative recurrence of rectal cancer was performed on 71 patients in a phase I/II clinical study from April 2001. With respect to the side effects of carbon ion radiotherapy, no acute phase or delayed reactions of Grade 3 or worse (NCI-CTC) were observed in the gastrointestinal tract, urinary tract, skin, etc. The treatment results were favorable; the local control rate was 86.4% at 3 years and 72.0% at 5 years and the overall survival rate was 64.0% at 3 years and 42.0% at 5 years.

Currently, carbon ion radiotherapy with a dose of 73.6GyE (49 patients) is being used as an advanced medicine. The 3-year local control rate is 90% and the 3-year survival rate is 75%, being comparable to the results of surgical resection and very favorable compared with conventional radiotherapy.

8) Pancreatic cancer

The incidence of pancreatic cancer has recently tended to increase, accounting for 6.4% of deaths from all cancers and ranking fifth most important in 1999. The main treatment for pancreatic cancer is surgical resection, but resection is indicated in only about 15% of all the patients with pancreatic cancer. Even in resected patients, the 5-year survival rate was as low as 18%, and the treatment results are the worst among gastrointestinal cancers.[25] The main factors worsening the prognosis are hepatic metastasis and retroperitoneal recurrence, which account for 50% of recurrences, and it is a major problem to control these.[26] In addition, unresectable pancreatic cancer accounts for 85% of the total, and the prognosis is extremely poor, and nonsurgical therapies such as radiotherapy and chemoradiotherapy are attempted.

Preoperative carbon ion radiotherapy for pancreatic cancer was started in a phase I/II clinical study in June 2000. The subjects were patients with infiltrative pancreatic cancers of stages I to IVa (Treatment Guidelines for Pancreatic Carcinoma, 4th edition) but those with A2, A3, Rp3, PV3, and N3 were excluded. In this clinical study, 22 patients were treated in a total dose of 44.8GyE and 48.0GyE/16 fractions/4 weeks. Histologically, all of the 15 resected patients showed a response of Grade 2 (considerable effect). Only

1 of the 22 patients including unresected cases has had a local recurrence (1 year and 2 months after treatment) to date. The 2-year survival rate was 23.8% in all patients and was 50% in patients in stage IVa, with no liver metas-tasis or peritoneal dissemination at surgery.

The above results showed that carbon ion radiotherapy could be safely performed as a preoperative treatment for pancreatic cancer with an improvement in local control to be expected. On this basis, a second clinical study in which the fraction number was reduced from 16 fractions to 8 fractions was started in April 2003 and is ongoing.

The second clinical study on carbon ion radiotherapy alone for locally advanced pancreatic cancer for which surgery is impossible was started in April 2003 and 36 patients were treated with the fractionation regimen of 38.4 to 50.4GyE/12 fraction/3 weeks until August 2006. A favorable effect was shown at a dose of 45.6GyE or higher with a local control rate of 93%, but the 1-year survival rate was not satisfactory at 44%. This was considered to be due to the early development of distant metastasis in the liver, and carbon ion radiotherapy has since been combined with a treatment that can control distant metastasis. A phase I/II study on a combined therapy for locally advanced pancreatic cancer with gemcitabine and carbon ion radiotherapy started in April 2006 and is steadily enrolling patients.

9) Advanced esophageal cancer (preoperative short-course irradiation)

Esophageal cancer is a disease in which recurrence is seen in about half of resected cases. Postoperative local recurrence decreases with adjuvant therapy but whether there is an improvement in the survival rate is not clear because of increased adverse events. However, prolonged survival periods were reported in patients who achieved histological complete response (CR) by preoperative treatment.[27,28] Thus, an improvement in the treatment results can be expected by combining a treatment having a high local effect and minimal adverse events with surgery.

Preoperative carbon ion radiotherapy in 20 fractions/5 weeks, previously used for locally advanced cancer, showed a high anti-tumor effect with acceptable toxicities in the surrounding normal tissue, but the recurrence outside the target volume, such as distant metastasis, was high and this treatment was terminated without the expected survival benefit.

We are now performing preoperative short-course carbon ion radiotherapy in 8 fractions/2 weeks on patients with operable esophageal squamous cell carcinoma of T1b to T3. In 24 patients treated since April 2004, no adverse events of Grade 3 or more due to carbon ion radiotherapy were observed. The histopathological effect was Grade 3 in 8 patients (33%) and Grade 2 or better in 20 patients (83%), indicating a greater effect with an increase in the dose. No recurrence within the irradiation field was observed but recurrence outside the field was noted in four patients. The 1-year and 2-year survival rate was 90% and 78%, respectively.

In this study, the optimal dose for preoperative radiotherapy will be determined based on the analysis of the long-term benefits including improvements in local control and survival rates. In addition, the treatment protocol on carbon ion radiotherapy alone or in combination with other modality will be designed.

10) Uterine cancer

The mortality from uterine cancer tends to decrease and the treatment results are relatively favorable when a combination of intracavitary brachytherapy and external beam radiotherapy is used. However, the treatment results for advanced uterine cancer are not satisfactory at present and this is the reason why new therapies such as chemoradiotherapy are indicated. Carbon ion radiotherapy has been used mainly for locally advanced tumors in an attempt to make a new breakthrough in treating tumors for which there has been almost no improvement in treatment results.

Three clinical studies have been conducted on carbon ion radiotherapy for cervical squamous cell carcinoma. Early in the clinical studies, several patients required surgical treatment because of severe complications in the intestinal tract. In the later part of the clinical studies, improvement in irradiation techniques improved the safety and dose escalation increased local tumor control. While a dose escalation study is still ongoing, carbon ion radiotherapy is considered an effective treatment for advanced cervical squamous cell carcinoma of stages III to IVa.[29]

Carbon ion radiotherapy for uterine adenocarcinoma has been limited to inoperable cervical adenocarcinomas with favorable local control rates being obtained. In the near future, we will include the radiotherapy for adenocarcinoma in the program of advanced medicine.

11) Ophthalmological tumors

Malignant choroidal melanoma

This is one of the important tumors for which carbon ion radiotherapy is indicated, but its prevalence is low in Japan. Eyeball enucleation has long been performed for this disease, but the 5-year survival rate is not good at about 60%. The rate of eyeball preservation after proton radiotherapy is about 90% when relatively small tumors for whom eyeball preservation is more likely are sele-cted and treated, while the rate is about 70% when all the patients are taken into account. Eyeball preservation as well as visual acuity preservation is difficult in patients with a large tumor and whose eyeball has to be extensively irradiated and in patients with a tumor near the macula or optic disc that has to be irradiated. Thus, if treatment results obtained with carbon ion radiotherapy are comparable to or better than those obtained with proton beam radiotherapy, the results will affect the selection of ion species in particle therapy facilities to be constructed in the future.

We started carbon ion radiotherapy using 5 fractions in a dose escalation study in April 2001 and have performed carbon ion radiotherapy as an advanced medicine since April 2004. A total of 72 patients had been treated until February 2007. In the early period, only highly advanced cases were treated to avoid sharing patients with the proton beam radiotherapy which was applied to less advanced cases. Although highly advanced cases predominated in carbon ion radiotherapy, the 5-year eyeball preservation was as good as 93%.[30] No recurrence within the irradiated field was observed in any patient and the improved anti-tumor effect was confirmed. A slightly higher rate of glaucoma in patients with a large tumor or a tumor near the optic nerve was observed. To reduce the risk of glaucoma in such cases, 2-field irradiation has been performed since April 2006 and subsequently glaucoma has not developed.

Lacrimal gland tumor

The incidence of this tumor is low but the prognosis is especially poor among ophthalmological tumors and a more effective treatment needs to be established. A dose escalation study on carbon ion radiotherapy using 12 fractions over 3 weeks was started in April 2002. To date a total of 14 foci (tumors) in 12 patients have been treated. No serious adverse reactions requiring eyeball enucleation were observed, the safety of the carbon ion radiotherapy was confirmed, and a high anti-tumor effect within the irradiation field was achieved. The marginal recurrence, however, was noted in four patients and it was found important to set a sufficiently large safety margin considering the nature of tumor progression. Further clinical study is needed to establish a more reliable technique with acceptable toxicities.

12) Central nervous system tumors

The standard treatment for malignant glioma is to reduce tumor burden as much as possible by surgical resection and then perform postoperative radiotherapy. Randomized trials have shown that radiotherapy in combination with chemoradiotherapy greatly improves the survival as compared to radiotherapy alone. Malignant glioma including anaplastic astroglioma and glioblastoma, like pancreatic cancer, is significantly difficult to control and two clinical studies have been conducted to date. In the first study started in October 1994, X-ray radiotherapy was given at 50Gy in 25 fractions over 5 weeks and ACNU was given at week 1 and at weeks 4 or 5, followed by carbon ion radiotherapy in 8 fractions in 2 weeks.[31] The carbon ion radiotherapy part of the treatment program served as a dose escalation study and patients were treated at 5 dose levels. It was demonstrated that both the local control and survival improved as the dose increased, confirming that the carbon ion radiotherapy was effective. There were no patients with late normal tissue reactions of Grade 3 or more in the brain other than the target volume. While the local effect was improved, the long-term survival is not yet satisfactory. A clinical study of carbon ion radiotherapy alone is thus ongoing and the accumulation of further cases is desired.

4. Discussion

NIRS started carbon ion radiotherapy in June 1994 using the carbon ion beam obtained from HIMAC. Clinical studies to develop appropriate irradiation techniques, thereafter fractionation regimens for various tumors were extensively conducted. Its approval as a highly advanced medical technology was obtained in October 2003 and the carbon ion radiotherapy was incorporated into general medicine. At NIRS, the 1st and 2nd meetings of the International Advisory Committee for Heavy Charged Particle Radiotherapy were held in 2003 and 2005, respectively, in which evaluations of treatment results and proposals for the future were made. In addition, an exchange of information with overseas facilities was made in order to propagate the clinical results obtained in NIRS and to support the charged particle radiotherapy projects of other facilities. We held the NIRS-MedAustron Joint Symposium jointly with the Medical University of Innsbruck in Austria in April 2004 and the NIRS-CNAO Joint Symposium jointly with the CNAO Foundation in Italy in November 2006. We concluded a memorandum for future study cooperation with both facilities.

Our experience to date is summarized as follows: Carbon ion radiotherapy is effective especially (1) in regions such as the head and neck (including eyes), skull base, lung, liver, prostate, bone and soft tissue, and the pelvic recurrence of rectal cancer and (2) for histological types such as adenocarcinoma, adenoid cystic carcinoma, hepatocellular carcinoma, and various types of sarcomas such as malignant melanoma and bone/soft tissue sarcoma, against which the photon beam is less effective. It is emphasized that (3) the short-course hypofractionated radiotherapy was effective against various tumors by using the advantages of biological dose distribution. In the lung and liver, very short-course irradiation allowing treatment to be completed in 1 or 2 fractions has been made possible. In addition, the short-course radiotherapy that is about half as short as the treatment time of conventional radiotherapy has become possible: e.g., 16-20 fractions/4-5 weeks for tumors of the prostate and uterus and 16 fractions/4 weeks for tumors of the head and neck and bone/soft tissue. For some tumors in the head and neck and pancreas, the prevention and treatment of distant metastasis are important to further improve the survival, and we have just started combination treatment with carbon ion radiotherapy and chemoradiotherapy. It is necessary to further improve the treatment results for malignant glioma, pancreatic cancer, uterine cancer, and esophageal cancer, for which clinical studies will be continued. In the early stages of the clinical trials developing treatments for tumors in the lower abdomen, some patients developed intestinal ulcers and perforations at high doses and required surgery, but similar types of severe complications were no longer observed after improvement in the irradiation techniques.

The number of patients treated with radiotherapy in Japan is about 160,000 per year and is expected to further increase. Since not only the number of patients treated but also the number of patients requiring sophisticated and advanced treatment may increase in the future, it is necessary to secure human resources and a wider range of physical resources to provide radiotherapy of higher quality. In this regard, the expectations for heavy ion radiotherapy, promising a high QOL, will be correspondingly higher

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《I》The past, present, and future of heavy ion radiotherapy studies

2. Outlook for clinical studies of heavy ion therapy

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The main purpose of clinical studies of heavy ion radiotherapy at the National Institute of Radiological Sciences (NIRS) is to evaluate the potential benefit of carbon ion radiotherapy to establish and make widely available methods for treating cancers with carbon ion beams safely and reliably. A further objective is to provide an effective cancer therapy to the general public. These aims are part of the national measures against cancer and are consistent with the Third-Term Comprehensive 10-Year Strategy for Cancer Control initiated by the Japanese Government in 2004. [1)]

The main objective of the Third-Term Comprehensive 10-Year Strategy for Cancer Control is to bring about a sharp decline in the incidence and mortality of cancer. An important research focus of the Strategy is the "development of innovative diagnostic and therapeutic methods" that involves programs to establish the clinical usefulness of charged particle radiotherapy and to reduce the size of radiotherapy equipment. NIRS is positioned as a core facility for cancer treatment studies using carbon ion radiotherapy in programs aimed at the "improvement of cancer medical technology and the creation of a supportive social environment" (Table I-2-1).

Based on the results that NIRS has obtained, we describe future prospects for clinical studies on heavy ion radiotherapy.

1. Results to date

Since 1994, when the first clinical study of cancer therapy with carbon ion beams was started, about 50 clinical studies have been completed with the aim of using the carbon ion beam for various cancers safely and effectively. These studies included the development of dose fractionation suitable for individual diseases, the development of irradiation techniques such as respiratory-gated irradiation, and the application of new diagnostic imaging methods, mainly positron emission tomography (PET), to cancer treatment as described in the preceding section. Clinical studies revealed that intractable cancers such as inoperable bone and soft tissue sarcomas can be cured and so can be cancers in the prostate, the head and neck, lung, and liver in a safe manner in a shorter treatment period. [2)]

The number of patients who have been treated with carbon ion radiotherapy at NIRS has grown to over 3,100, and our therapy has been officially approved as a highly advanced medical technology in 2003. Although the introduction of carbon ion radiotherapy as a highly advanced medical technology led to a higher cost burden for the patient, the number of patients treated each year has recorded a sustained growth over the past few years. The patient intake target for the current mid-term plan (2006 to 2011) had been set at 500 and was already achieved in the first year. To make the treatment more affordable, however, a study was undertaken in an effort to reduce equipment size and cost. This study has already produced a therapeutic system only about 1/3 the size and cost of the present HIMAC. A prototype of the system is currently under construction at Gunma University, with the expectation that it will be possible to start cancer treatment with it in 2010. A basic technology study designed to develop an irradiation system with scanning and rotating gantry supports adaptive to respiratory movement is underway to meet the challenge of creating next-generation heavy ion irradiation equipment. This project aims to achieve great cost reduction that comes as a complete surprise.

Nearly 4,000 patients had been treated with charged particle radiation in three facilities worldwide by the end of 2006. The therapeutic results are internationally acknowledged. A considerable number of charged particle therapy systems are under construction, mainly in industrialized European countries, offering the promising prospect of achieving more reliable and safer cancer therapy in the near future. [3)] This underscores the significance of the contribution NIRS has been making to charged particle therapy, a treatment modality that has earned NIRS worldwide recognition for its leading role in fighting against cancer.

Table I-2-1 The position of carbon ion radiotherapy in the 3rd Term Comprehensive 10-Year Strategy for Cancer Control

The Third Term Comprehensive 10-Year Strategy for Cancer Control (July 25, 2003)

1.Promotion of cancer research
Main research projects
(4) Development of innovative diagnostic and therapeutic methods
8)Establishing the clinical usefulness of particle ion therapy and reducing the size of therapeutic equipment…
2.Promotion of cancer prevention (omitted)

3.Improvement of cancer medical care and creation of a supportive social environment
(1) Reinforcement of core base functions for cancer study and treatment
… Research and development of radiotherapy such as carbon ion radiotherapy is performed mainly by the National Institute of Radiological Sciences.

(Cited from the website of the Ministry of Health, Labour and Welfare)

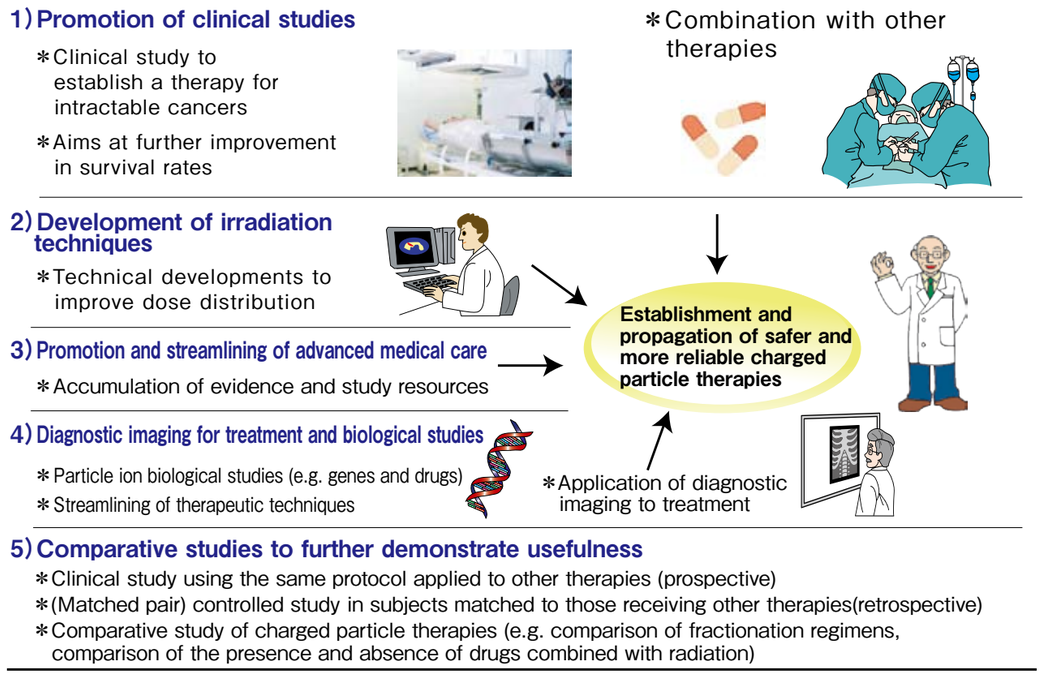
2. Future approaches

Neither current surgery, radiation, nor anticancer agents for treating cancers is perfect, and clinical studies are continually being undertaken in order to find better therapies. While the clinical studies conducted at NIRS over the past 10 years established the basic usefulness of charged particle therapy, clinical studies aimed at developing the next-generation of therapies have already started. Table I-2-2 summarizes our specific approaches to future clinical research on charged particle therapy.

1) Promotion of clinical studies

Previous clinical studies enable us to use carbon ion radiotherapy for various cancers safely and effectively. Satisfactory therapies

Table I-2-2 Clinical research on charged particle therapy: future approaches



have not yet been established for intractable tumors such as pancreatic cancer and brain tumors, and clinical studies need to be continued to find and establish better therapies. Local control is required to cure cancer, and good local control has been achieved with carbon ion beams. Depending on the type of cancer, however, improving local control does not always prolong the survival period. In locally advanced malignant melanoma, in particular, long-term survival was not always obtained although local control had been significantly improved with carbon ion radiotherapy. There are patients who, although good local control is obtained, do not attain long-term survival because distant metastasis develops or second and third foci (colonies) sometimes occur. To improve long-term survival, we have used carbon ion radiotherapy in combination with anticancer agents and have obtained favorable results.

We have established safe methods for carbon ion radiotherapy for many patients with inoperable cancers. As the next step, it will be necessary to develop therapies for improving survival rates, seeing that cancer is a systemic disease.For malignant melanoma, pancreatic cancer (inoperative cases), and prostate cancer (high-risk group), we use a treatment protocol in which satisfactory control is achieved with carbon ion radiotherapy, and distant metastasis is treated with chemotherapy to improve survival rates. In future heavy ion radiotherapy studies, we will try to improve the quality of local control that can be achieved with heavy ion radiotherapy and to improve the overall therapeutic results.

2) Development of irradiation techniques

Despite the dose convergence property that is unique to the heavy ion beam, adequate treatment may be difficult or irradiation with a sufficient dose may be impossible because of the relationship between the focus (therapeutic target) and the surrounding organs. Thus, for example, patients with cancers that are in contact with, or which infiltrate, the gastrointestinal tract may develop severe side effects such as gastrointestinal perforation. Early in our dose escalation study such serious side effects occurred in the high dose groups, requiring emergency hospitalization. In these patients, colostomy was performed prior to radiotherapy or a spacer was inserted to avoid the gastrointestinal tract, or in some cases, both procedures were performed, resulting in an increased number of indications. These techniques are applicable to ordinary radiotherapy as well as to charged particle therapy and lead to the development of less harmful, effective methods.

A great advantage of charged particle therapy is that it permits the selective irradiation of different lesions. Stacked conformal radiotherapy, a new scanning irradiation method adaptive to respiratory movement, and an on-demand irradiation system sensitive to day-to-day changes in the tumor or body have been developed to obtain better dose distribution. To make these advances, cooperation with clinical facilities is indispensable.

3) Promotion of advanced medicine

NIRS applied the irradiation therapies that had already been proven safe and effective in clinical studies to the development of its advanced medicine. The therapeutic application of our advanced medicine led to an increase in patient enrollment and provided more evidence to substantiate the efficacy and safety of carbon ion radiotherapy. Carbon ion radiotherapy has been recognized as a standard therapy for many diseases for which other therapies are problematic. The results of the use of advanced medicine as a modality indicated for certain diseases have corroborated the validity of charged particle therapy. Analysis of the outcomes for patients treated with advanced medicine provides much food for thought in planning new clinical studies. A case in point is that analysis of data from patients subjected to advanced medicine for malignant melanoma, which is a relatively rare disease, revealed that tumor size is an important prognostic factor. This discovery led to new therapeutic studies.

Carbon ion radiotherapy is performed only in two institutions in Japan, and as the number of patients treated continues to rise at a dramatic rate, there is an increasing demand for greater treatment efficiency. In this respect, short-term hypofractionation is effective and greatly contributes to the effective utilization of restricted resources. Very short-term irradiation consisting of only one or two sessions developed for lung and liver cancer has been adopted internationally and the extension of this technique to other cancers is desirable. Studies have already been initiated to develop short-term irradiation modes for regions other than the lung and liver by analyzing data obtained from previous application instances of advanced medicine. The specific practice is to set up groups with different irradiation periods and different numbers of irradiation fractions for the same disease and then conduct randomized comparative inter-group studies to determine the most efficient irradiation period.

Once the indications for carbon ion radiotherapy have been determined, necessary pre-treatment preparations are made, including fixture preparation, CT scanning for treatment planning, execution of the treatment plan, preparation of a bolus (compensator) and collimator, and treatment rehearsal. The conduct of all of these operations has been improved over the past 10 years, and they can now be performed rapidly and easily without detriment to accuracy. During actual irradiation we identified certain problems (such as the positioning of the irradiation field) requiring the most time and then undertook research and technical development to shorten the time required for these actions during treatment. Technical development for further streamlining treatment is ongoing and will remain one of the most important research concerns even in the future.

The annual number of treatments at NIRS is about 600, and the total number of patients registered exceeds 3,100. The amount of medical information on the patients already treated in addition to those who have been newly registered is vast and the construction of a medical information database to process the data efficiently and appropriately is also an important research subject.

4) Diagnostic imaging for treatment and biological studies

Advanced diagnostic techniques have played a major role in the improvement of therapeutic results and their further advancement is highly desirable. The introduction of new diagnostic equipment, such as PET, multidetector computed tomography (MDCT), and high-field MRI, enables early small cancers to be accurately diagnosed. To utilize the information for actual carbon ion radiotherapy, it is necessary to consider not only the relationship between the focus (tumor) and the surrounding organs, but also the integration of different images and the deformation and movement of organs associated with respiration. Specific studies may include early assessment of therapeutic effects and analysis of prognostic factors by combining various diagnostic imaging techniques and creating fusion images. The studies may also include advancement of treatment planning by utilizing imaging equipment that temporally traces the dynamics of fusion images and 4-dimensional CT. Recently, imaging of the state of oxygen as well as the sugar and amino acid metabolism in the tumor has become possible and an important research issue in the near future will be how these techniques can be applied to treatment.

In various biological studies to further enhance the effectiveness of carbon ion radiotherapy and verify the safety, samples and data obtained from the clinical studies on carbon ion radiotherapy are indispensable and close cooperation is important. Clinical application of both the knowledge obtained from these studies and drugs (e.g., anticancer agents, sensitizers, and protective agents) to improve treatment outcomes is also a target of clinical research.

5) Comparative studies

Comparative studies, already feasible at present, to further clarify the usefulness (indications) of charged particle therapy include those in which the same protocol is applied to other therapies, the backgrounds of subjects are matched, and treatment desired by study participants is offered. In such cases, consent from study participants is easily obtained, study costs are low, and agreement among participating facilities is relatively easily obtained since the treatment desired by each patient is provided on the basis of cooperation with other institutions. Another method is to determine the inclusion criteria for patients already treated and then to comparatively analyze the therapeutic results in a matched pair study. This is feasible if consent is obtained from the institutions that perform the therapies being compared.

When comparing various therapies, the results of randomized controlled studies provide the strongest evidence at present. Theodore S. Lawrence, editor of the Journal of Clinical Oncology, has made the following statement about the need for randomized controlled studies when comparing different therapies, or different types of therapeutic equipment, in the field of radiation oncology: [9]

"In medical oncology, there is a need to compare drug treatment A to drug treatment B. It is not possible to determine which is better without carrying out a randomized trial. In radiation oncology, one can know, based on physics, that protons deliver a better dose distribution than photons or that IMRT is superior to three-dimensional conformal therapy. If treatment planning and delivery

are carried out properly, which can be defined by a set of rules, there is no debate; this is a matter of physics. The big question is: is the clinical improvement worth the added expense? What kind of trial needs to be designed to answer this question? It will be difficult to run a randomized trial in the United States asking whether a treatment that is superior based on physics is worth it. Would patients permit themselves to be randomly assigned to the standard but less expensive therapy?"

Previous progress in radiation oncology is inextricably linked to the development of irradiation equipment, but no randomized controlled study has been conducted for the purpose of the introduction of new therapeutic equipment. No randomized controlled study was conducted in the shift from cobalt irradiation equipment to linac X-ray systems, but if that had been done there would have been little difference between the cobalt and the linac in the treatment results in patients with early laryngeal glottic cancer. Cobalt irradiation has advantages in terms of both cost and equipment maintenance, and the results of linac X-ray irradiation may be poor unless the correct energy is selected. Cobalt irradiation is sufficient to treat laryngeal cancer, and it is unnecessary to introduce linac irradiation to achieve successful treatment for this cancer. However, almost no treatment with cobalt is performed in developed countries. The distribution of the very-high-energy X-rays of the linac allows safer treatment of foci (tumors) existing at a deep site, and the design of a study to determine the difference between cobalt and linac irradiation in patients with laryngeal cancer is itself a problem.

Randomized controlled study protocols should be considered for studies aimed at making the usefulness of carbon ion radiotherapy clearer and which may lead to more efficient operation, such as extended indications of short-term hypofractionation, or to more effective treatment and improved local effect. However, at present, most of the patients receiving carbon ion radiotherapy visit the clinic looking for this treatment, and it is difficult to obtain consent for a randomized controlled study from patients. It is difficult to conduct a randomized study between different types of equipment even in the United States, where the use of randomized controlled studies is advanced; it is equally, if not more, difficult in Japan, too.

Accordingly, future comparative studies on heavy ion radiotherapy, as shown in Table I-2-2, 5), "Comparative studies aimed at making the usefulness of carbon ion radiotherapy clearer," are as follows:

(1) Clinical studies using the same protocol applicable to other therapies,

(2) Matched-pair controlled studies in subjects matched to those receiving other therapies, and

(3) Comparative studies comparing different charged particle therapies.

3.Conclusion

In Japan, the number of patients with cancer increases steadily with the rapid aging of the population. The development of therapies to cure cancer with safety and assurance, and with less suffering, even among the elderly, is strongly desired by the Japanese people. Owing to the results of previous studies, carbon ion radiotherapy has been recognized as a treatment that can achieve this goal. Studies conducted over the past 10 years have made it possible to reduce the cost of a carbon ion radiotherapy system to about 1/3 that of the HIMAC. Next-generation carbon ion radiotherapy equipment will provide more advanced treatment at a drastically reduced cost. To achieve this, cooperation between equipment manufacturers and NIRS is indispensable, and government support is critical.

Future heavy ion radiotherapy will provide cancer treatment with less suffering for many intractable cancers using more advanced irradiation systems and recent molecular biological techniques.

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《I》The past, present, and future of heavy ion radiotherapy studies

3. Patients treated with carbon ion radiotherapy

Director of the Research Center Hospital for Charged Particle Therapy
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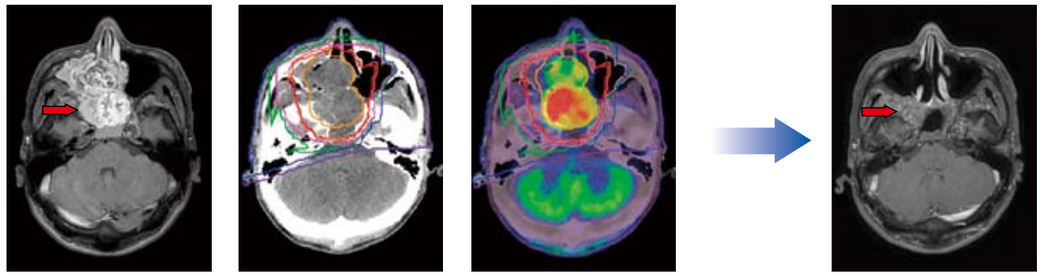
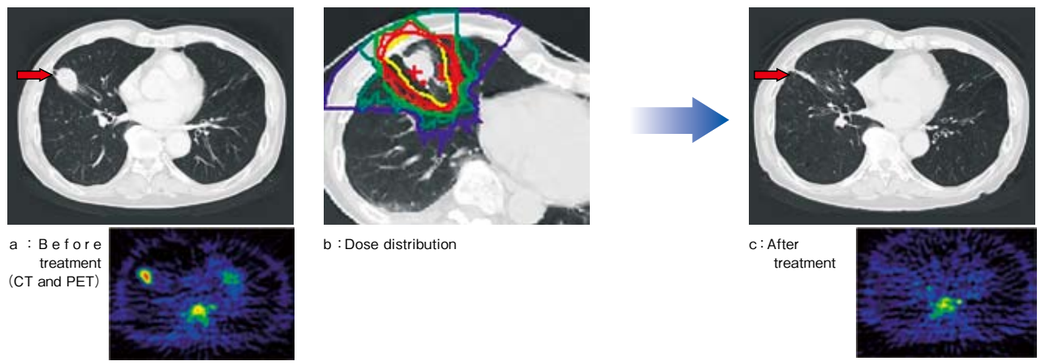
Cases treated with charged particles



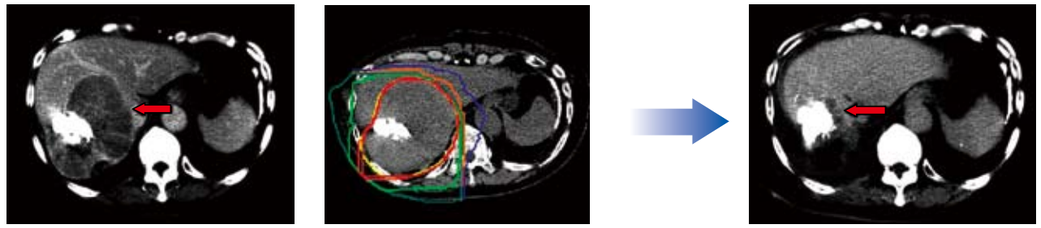
a : Before treatment　b : Dose distribution (CT)　c : Dose distribution (CT and PET)　d : After treatment

Fig. I-3-1 Head and neck cancer (adenoid cystic carcinoma). After irradiation with 57.6GyE/16 fractions/4 weeks, the tumor disappeared almost completely.



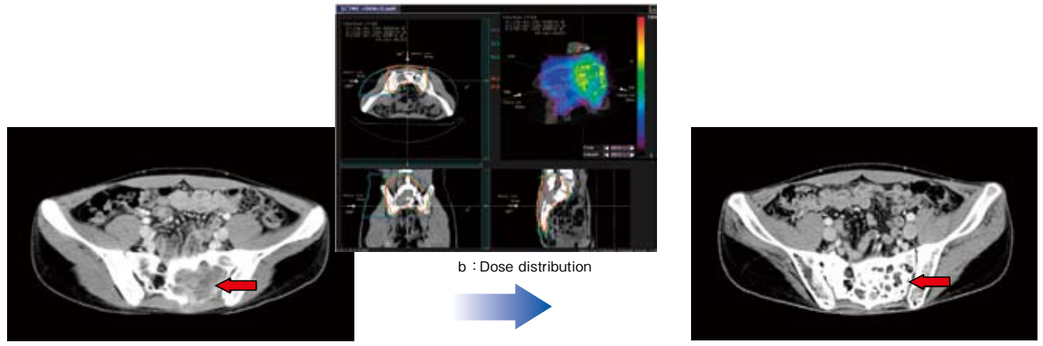
a : Before treatment (CT and PET)　b : Dose distribution　c : After treatment

Fig. I-3-2 Lung cancer, stage I (T1N0M0). After irradiation with 34.0GyE/1 fraction, the tumor disappeared almost completely.



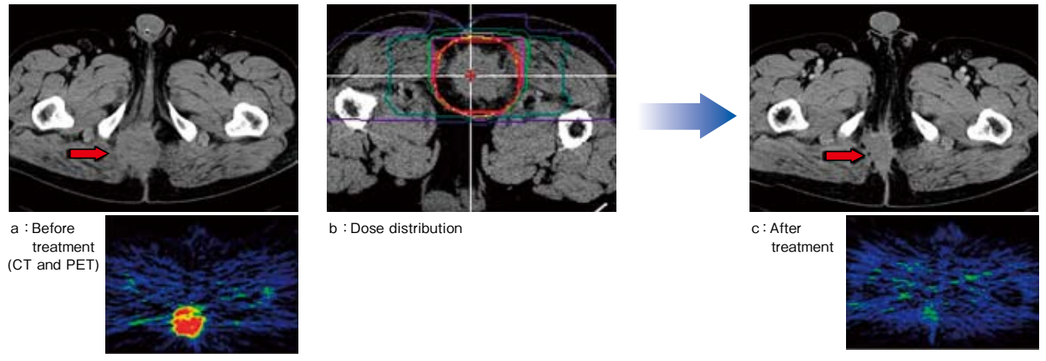
a : Before treatment　b : Dose distribution (CT)　c : After treatment

Fig. I-3-3 Recurrent tumor after other therapies for a hepatocellular carcinoma of 11.2cm in maximum diameter. After irradiation with 52.8GyE/4 fractions, the lesion disappeared almost completely.



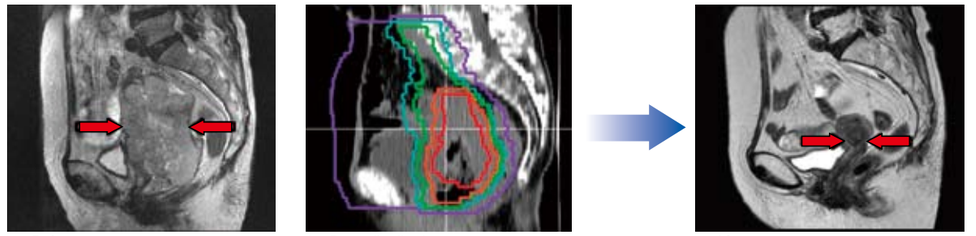
a : Before treatment　b : Dose distribution　c : After treatment

Fig. I-3-4 Sacral sarcoma. After irradiation with 64 to 70.4GyE/16 fractions, bone destruction region (arrow) is replaced by calcification.



a : Before treatment (CT and PET)　b : Dose distribution　c : After treatment

Fig. I-3-5 Rectal cancer (postoperative local recurrence). After irradiation with 73.6GyE/16 fractions, the tumor decreased in size markedly and PET showed that the abnormal accumulation of FDG had disappeared.



a : Before treatment　b : Dose distribution　c : After treatment

Fig. I-3-6 Cervical squamous cell carcinoma, stage IIIB (12 × 8cm). After irradiation with a total dose of 68GyE, the tumor disappeared almost completely.

《Ⅱ》**Research and development of heavy ion radiotherapy systems**

1.Development of a standard type of carbon ion radiotherapy system

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Introduction

Carbon ion radiotherapy has now become a worldwide recognized cancer therapy. This recognition has been achieved through the pioneering studies carried out at the Lawrence Berkeley National Laboratory (LBL) in the USA for two decades from the end of the 1970s, [1] and the subsequent full-scale clinical studies conducted by the National Institute of Radiological Sciences (NIRS) performed over a 13-year period,[2] as well as the clinical treatments provided by the Gesellschaft fuer Schwerionenforschung mbH (GSI) in Germany from the latter half of the 1990s.[3] The number of patients treated by the NIRS exceeds 3,100 and the NIRS has tried to treat tumors not only in the head and neck but also in various regions all over the body. In these clinical studies, very favorable therapeutic results were obtained, and it is now one of our goals to extend the benefits of carbon ion radiotherapy to a larger number of people. Clinical studies at the LBL and GSI used accelerators constructed for high-energy physics research. The HIMAC of the NIRS is a facility built mainly for the purpose of cancer treatment. It is old equipment, the design process started in the latter half of the 1980s and construction was completed in 1994. As unique equipment in the world at that time it enabled extensive medical studies on heavy ion radiotherapy but it is very expensive equipment for the present purpose to perform carbon ion radiotherapy. The next step required to provide heavy ion radiotherapy in all areas of Japan is to develop new safe and efficient carbon ion radiotherapy equipment that is cost effective and clinically practical.

First, the construction cost of the new equipment should be very much lower than the 32.6 billion yen cost of the HIMAC. In addition, energy consumption should be greatly reduced and maintenance and operation of the accelerator facility by a small number of personnel should be possible. These specifications should greatly reduce both construction depreciation and operational costs compared with those of the HIMAC. In addition, a system that allows efficient treatment is required.

Based on the above requirements, in 2004, the NIRS began to design and develop a standard type of the equipment fully utilizing the experience gained with the HIMAC, and completed verification tests on individual elements of the technology using actual carbon ion beams in 2006. Based on the results, the first standard type facility that will play a role in the demonstration of production carbon ion radiotherapy equipment is under construction at Gunma University. In this article, we describe the details of this standard type facility.

Specifications for standard type of carbon ion radiotherapy facilities [4,5]

The whole area for the standard type of carbon ion radiotherapy facility is estimated to be about 50m × 50m because of the limitations of most hospital premises. For the accelerated particle, only carbon ions are to be accelerated to fully utilize the treatment experience with the HIMAC. The target regions are to cover all the regions treated with the HIMAC. The minimum requirement is to be able to treat bone and soft tissue tumors that are difficult to cure completely with other therapies.

Beam energy

The maximum internal range of the carbon ion is set at 25cm, to the same as that of the HIMAC. The internal range depends on not only beam energy but also the field-forming technique. Since the loss of the range can be reduced to 2.5cm or less in the spiral wobbler method, [6] the maximum energy needed to obtain the internal range of 25cm is set at 400MeV/n. The minimum energy is set at 140MeV/n for ocular treatments, which require the smallest internal range.

Field size and dose rate

The maximum field size is set at 22cm in diameter and the maximum spread-out Bragg peak (SOBP) at 15cm, parameters the same as those of the HIMAC. The actual field is determined by the size of the maximum opening of the multi-leaf collimator and is 15 cm × 15 cm. The dose rate was set at 5GyE/min/L similar to the same as of the HIMAC. If the beam efficiency at the field port is 30% (typical efficiency in the spiral wobbler), this dose rate is calculated at about 109 pps in the entrance of the field port, which is about half the beam intensity of the HIMAC.

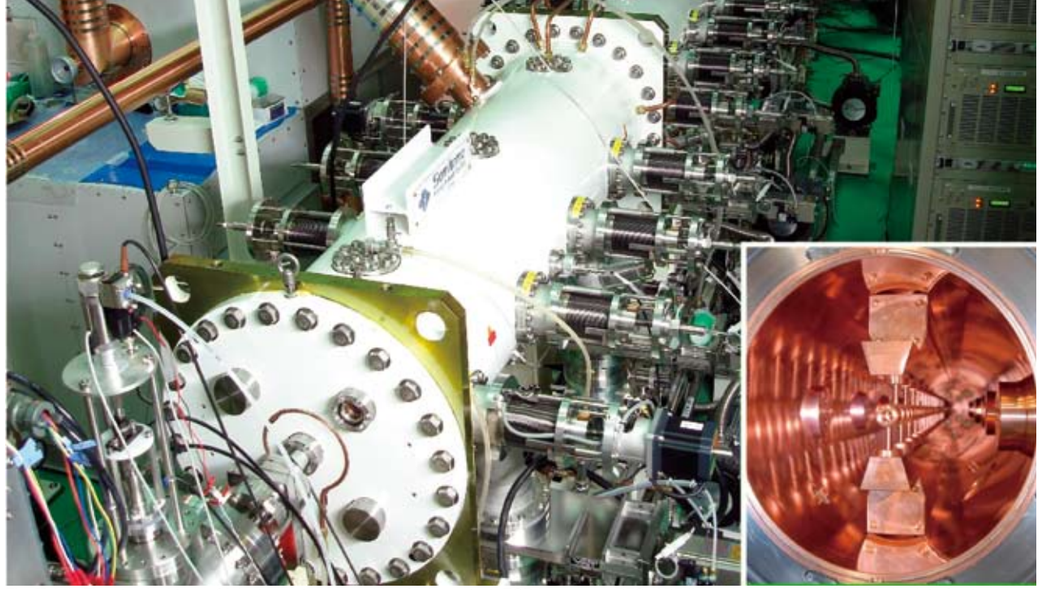

Fig. II-1-1 The standard type of injector system assembled for beam test: ECR ion source, RFQ, APF-IH, and analysis unit; from the back to front

Numbers of irradiation ports and irradiation rooms

The average number of fractionated irradiations in clinical studies or treatment with the HIMAC is 12, and the average time from the patient's entrance into the irradiation room to their exit is about 25 minutes. If the time available for therapeutic irradiation each day is 6 hours (in the HIMAC about 2 hours is used for dosimetry) and the number of operating days per year is 240 (5 days/week × 48 weeks/year), the annual number of patients treated in one room is estimated at 288. Thus, approximately 900 patients per year can be treated in three rooms. Because the ratio of horizontal ports to vertical ports used in the HIMAC is 5:4, the standard type of the facility consists of the three rooms: a horizontal port room, a vertical port room, and a horizontal/vertical port room. To cope with further increase in the annual number of treatments, we attempt to design the facility to switch the beam course and energy within one minute. The above estimate of patient numbers treated per year is based on the operation of the HIMAC, but about 2,000 patients per year can be treated if we specialized in treatment and operated from 7 a.m. to 11 p.m. as at the facility at the Loma Linda University, California. The annual number of treatments should be estimated, considering all aspects of the capacity of the facility, including the time for diagnostic imaging, treatment planning, fixture production, treatment simulation, bolus and patient collimator production, as well as the number of treatment rooms.

Composition of the accelerator and beam energy

The accelerator system is composed of the injector, consisting of a very easily maintained Electron Cyclotron Resonance (ECR) ion source and a compact Radio-Frequency Quadrupole (RFQ linac) plus an Alternating Phase Focusing (APF) drift-tube linac (DTL) with high power efficiency, and a synchrotron. Based on the beam intensity schedule for attaining the above dose rate, the output current of the ECR ion source is 260eμA or more at C^{4+}. To inhibit the space charge effect and inject efficiently into the RFQ, the energy was increased from the 8keV/n used in the HIMAC to 10keV/n. The output energy of the injector was set at 4MeV/n, considering the space charge effect in the synchrotron and the efficiency in the stripper (charge state converter). Thus, the synchrotron has an injection energy of 4MeV/n and a maximum energy of 400MeV/n.

Selection of irradiation methods

To minimize cost by reducing the risk in design and produce, the field forming method for the standard type equipment was based on the broad beam method, with which we have much experience in the HIMAC. To reduce the beam energy as much as possible and downsize the equipment, a spiral wobbler method with small loss of range was developed. In addition, respiration-gated irradiation and stacked conformation radiotherapy were adopted.

Maintenance

Hospital carbon ion radiotherapy facilities are expected to have greatly reduced maintenance costs. Since the installation and operation of the facility may vary greatly with the role of the hospital in each area, it is difficult to accurately estimate the construction cost and operating cost without specified conditions. The following is an example when a local core general hospital introduces minimal specification equipment to its premises.

If the existing basic equipment such as diagnostic equipment and transformer (electricity) facility is used, the construction cost of the equipment and building is about 10 to 12 billion yen, and the depreciation cost taking into account the depreciation periods is about 500 million yen. The utility cost for operating the equipment is nearly 300 million yen per year, and the maintenance cost of the equipment and building is estimated at about 400 million yen per year. The personnel cost is nearly 300 million yen per year for new occupations such as medical physicists and engineering technicians. The costs for any necessary increase in the number of medical staff such as physicians and nurses are not included here since they may vary greatly depending on the existing staffing of the hospital. In total, the annual cost is about 1.2 billion yen if there are no additional land costs and no interest charges assuming that construction is possible without the need to borrow funds.

The treatment cost per patient is about 1.5 million yen when about 200 thousand yen for the consumables required for each patient is added to the above total annual cost divided by the annual number of patients treatable. This per patient cost will be higher if there are increased costs for medical staff, land costs, and interest charges. While a more accurate estimate should be made by comprehensively considering what disease is to be treated in the area and which systems are optimized, the costs to individual patients may decrease steadily.

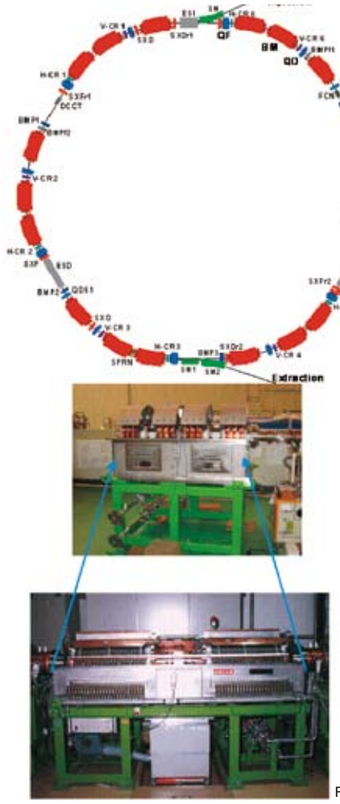

Fig. II-1-2

New technologies developed for the standard type of carbon ion radiotherapy equipment

10-GHz ECR ion source [7]

The injector system of the standard type consists of a 10-GHz ECR ion source, RFQ linac, and an APF-IH linac; it accelerates the C^{4+} beam to 4MeV/n, converts the charge to C^{6+} with the stripper (charge state converter), and injects the beam into the synchrotron.

The 10-GHz ECR ion source has been continuously developed at the NIRS for about 10 years. Its main features are that the plasma confining magnetic field is generated by permanent magnets alone, and that the deviations from the designed magnetic field can be compensated for by tuning the frequency of a traveling-wave tube amplifier. It is very compact with a diameter of about 30cm but can generate C^{4+} of 400eμA (extraction voltage, 30kV) or more with a microwave of 300W. It is an excellent ion source almost free from the need for maintenance.

High-efficiency linear accelerator [8,9]

The newly developed high-efficiency compact linear accelerator (APF-system IH-type DTL) is 6m long and is not only much shorter than the linear accelerator in the HIMAC, over (32m) , but also greatly reduces costs by a reduction of the number of high-power radio frequency amplifiers and a design to cut down power consumption dramatically. The acceleration principle of the IH-type DTL was invented in the 1950s, but it was not possible to accurately calculate the voltage distribution and technology has scarcely been put into practical use. The use of a 3-dimensional electromagnetic field calculation program enabled the electromagnetic field distribution to be directly calculated, which also enabled a resonator to be designed. In addition, the alternating phase focusing (APF) system was adopted to converge the beam during acceleration. Since both of beam convergence and acceleration are made in the radio-frequency electric field alone, it is unnecessary to incorporate a focusing element such as the conventional quadrupole magnet into the resonator. This not only decreases the construction cost of the equipment but also simplifies beam adjustment greatly, resulting in a reduction in the running cost. To facilitate the actual beam adjustment, a new and precise electric field adjustment method using an inductive tuner and an automatic tuner control method to keep the resonance frequency constant without disturbing the electric field distribution was developed.

The injectors, based on the above design, were constructed and the beam trial was performed. The stable performance with acceleration energy of 4.0MeV/n, energy resolution of ±0.4 %, normalized 90 % emittance of 1.0πmm・mrad, LEBT (Low Energy Beam Transport) RFQ, and APF-IH-combined transmission efficiency of 79% was obtained as expected, and we were the first in the world to successfully put the injector system using APF-IH into practical use.

Synchrotron [10]

The synchrotron was designed to accelerate from entrance energy 4MeV/n to a maximum of 400MeV/n. The lattice structure was based on FODO, and three bending magnets were placed into one unit to reduce size. Its circumference is 63m, being smaller than the 77.6m of the PIMMS synchrotron (400MeV/n) designed by the Organization Europeen pour la Recherche Nucleaire (CERN) and the 93.6m circumference of the PATRO synchrotron (380MeV/n) in Hyogo, Japan, and similar in size to the HIT synchrotron (430 MeV/n) of the GSI.

The multi-turn injection method was used to increase the beam intensity and achieve the number of high-intensity accelerated particles. An auxiliary coil was installed in some sextupole magnets to correct the space charge at injection. For the longitudinal beam structure, a flat distribution is achieved by changing beam duration and injection timing. In addition, a high-performance magnetic material core using a cobalt-based amorphous material with excellent frequency properties was developed for the radio-frequency acceleration cavity[11] so as to produce accelerating voltage waveforms to accelerate the longitudinally flat beam. This un-tuned RF cavity is about half the size of that in the present HIMAC and is designed to output 4.5kV at an RF power of 8kW in the frequency range of 0.4 to 7.0MHz. Such a low input power allows driving with a transistor amplifier without vacuum tubes. This is a great advantage in terms of maintenance. We installed this cavity into the HIMAC and successfully completed an acceleration test and achieved higher harmonics operation.

Irradiation port [5,6]

A spiral wobbler method with a smaller range loss than the single wobbler method used in the HIMAC has been developed. This is a method of forming an irradiation field by rotating along a spiral trajectory in a target plane, the broad beam in the form of Gaussian with a standard deviation of 25mm (in terms of the density distribution) by multiple scattering. To draw a spiral track, amplitude modulation was added to the wobbler frequency. The NIRS produced a test port and conducted a beam test. The beam test was conducted under conditions in which the wobbler rotation frequency was set at 59Hz, the current amplitude was increased with the square root of time, and the test was repeated at an amplitude modulation frequency of 23Hz. The most difficult problem was whether a power source such as a high-power function generator could be produced. This was initially very difficult, but finally a uniform irradiation field of 22cm in diameter was successfully formed. Next, we made the wobbler current waveforms triangular to try a raster scan and successfully obtained

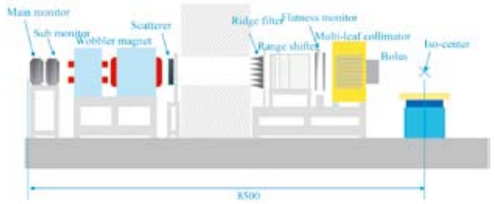

Fig. II-1-3 Layout of the irradiation port of the standard type of equipment

Special issue Up-to-date results of heavy ion therapy - present status and the future -

an irradiation field similar to that in the spiral wobbler method. These field forming methods have the great advantages of higher beam use efficiency due to a larger proportion of the uniform field and the reduction in the size of the equipment in addition to smaller range loss over the single wobbler method.

After developing and testing each element of the technologies incorporated in the irradiation port equipment, we designed and produced a prototype irradiation port. This is shown in Fig. II-1-3.

Fig. II-1-4 Bird's-eye view of a standard type of clinical facility under construction in Gunma University

Treatment planning

The Heavy Ion Treatment Planning System (HIPLAN) used by the NIRS was developed by the NIRS based on equipment developed by the Lawrence Berkeley National Laboratory (LBL) in the 1980s. It is a very flexible system but is specialized for use with the HIMAC and is not compatible with the new equipment for standard type. Thus, the NIRS has to plan to develop a new scanning method and treatment planning system compatible with the standard type of radiotherapy equipment as part of the next stage of the overall program. The basic requirement for new treatment planning equipment is that the NIRS should incorporate its own functions while following international standards as much as possible. Heavy ion radiotherapy itself is still developing, and there is a strong possibility that new irradiation methods and therapies will be developed and heavy ion radiotherapy will become more and more advanced. It is essential that the basic treatment planning system be capable of continuous improvement to cope with these advances. Functions common to general radiotherapies other than charged particle radiotherapy should always have a higher performance and quality than the standard for the industry.

Based on the above consideration , we have adopted a method in which a commercially available treatment planning system is loosely linked to external equipment required for heavy ion dose calculation to configure the total system. Separate external dose calculating equipment is used so that the newest particle ion technologies could be incorporated. A dose calculation code for broad beams developed by the NIRS and a calculation code for an advanced irradiation method compatible with respiration-gated irradiation are incorporated to create an environment for facilitating future developments.

A standard type of carbon ion radiotherapy facility to be constructed at Gunma University

We have developed a standard type of carbon ion radiotherapy equipment and treatment therapies suitable for clinical application and have gradually transferred the technical results obtained to commercial companies to remove the risks inherent in equipment development from the university and to reduce the equipment costs. We have produced a model building design for a clinical facility to house the equipment, including the optimal shielding design using up-to-date radiation shielding codes, and the layout of the machine room and the power source room to reduce the building construction cost. New technologies developed in the creation of the next-generation irradiation system will be gradually incorporated into the clinical equipment. We have investigated technologies providing higher performance at lower cost and developed high-performance cancer therapy equipment suitable for use in clinical facilities that can be installed at a cost of 10 billion yen maximum including buildings, and which may be installed for as little as 8 billion yen in about 10 years time.

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《Ⅱ》**Research and development of heavy ion radiotherapy systems**

2.Research and development of the next-generation irradiation systems

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Introduction

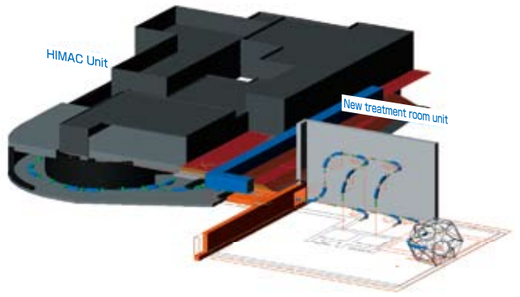


Fig. II-2-1 The planned layout of the New Treatment Unit

Thirteen years have passed since the start of clinical studies with the HIMAC using carbon beams on June 21, 1994, and more than 3,100 patients with cancer have been treated. During this time, we have improved therapeutic accuracy and streamlined treatment with favorable results through research leading to the development of new accelerator and irradiation technologies such as 2-dimensional respiration-gated irradiation[1] that allows the irradiation of a target moving due to respiration and layer stacking irradiation stacked to reduce exposure of normal tissues near the skin to unnecessary irradiation.[2] However, high-precision treatment irradiation using 3-dimensional scanning of moving targets, such as a target that decreases in size from the start to the end of treatment, a target whose position changes by the day due to the effect of cavities, and a target moving due to respiration or heart beats, has not yet been achieved anywhere in the world although it is a strongly desired goal. If we succeed in developing this moving target 3-dimensional scanning method, we will pioneer both adaptive heavy ion radiotherapy, i.e. irradiation treatment responding to the state of the cancer under the treatment, and the high-precision irradiation of moving targets, resulting in further improvements in the therapeutic outcomes. With further improvement in dose convergence caused by reduced patients' suffering and optimized multi-port irradiation in combination with the use of a rotating gantry, the dream of one-day-visit treatment will come true. In addition, pinpoint irradiation to focus the dose on highly radioresistant hypoxic cells will be made possible following the advancements in molecular imaging techniques, and the day when these will be applicable to patients with very intractable cancers considered incurable will come soon. It is our mission to further advance heavy ion radiotherapy to meet these goals. To this end, the Research Center for Charged Particle Therapy organized the "Medical Physics Research Group" and started research and development of the next-generation heavy ion radiotherapy irradiation system in fiscal 2006. Here, the term next-generation heavy ion irradiation system refers to rotating gantry irradiation equipment as well as 3-dimensional scanning irradiation equipment adaptive to a fixed target and to respiratory movement. Our research objectives are shown below.

3-dimensional scanning method
1) Development of high-precision irradiation without collimators
2) Development of a 3-dimensional scanning method adaptive to moving targets

Rotating gantry
1) Reduction in patient's suffering from positioning and treatment
2) Improvement in the flexibility of treatment planning

This project plans to extend the beam line from the HIMAC to a new treatment facility to enable the establishment of the next-generation irradiation system without disturbing the current treatment program using the HIMAC. As shown in Fig. II-2-1, this new treatment facility consists of two irradiation rooms with a horizontal and a vertical irradiation port equipped with 3-dimensional irradiation equipment, and a rotating gantry room. The heavy ion beams are supplied from the upper synchrotron of the HIMAC.

In this paper we outline the past research and current development of next-generation irradiation systems.

Development of the respiration-gated 3-dimensional scanning method

In general, the therapeutic results of radiotherapy depend on giving a uniform and sufficient dose to the tumor while minimizing the exposure of surrounding normal organs. In the broad-beam irradiation method used in the HIMAC, and in charged particle radiotherapy facilities in other institutes, a narrow beam with a Bragg peak from the accelerator is spread with a scatterer and wobbler magnet in the transverse direction and with a ridge filter to control the depth of the beam to cover the target. The beam is shaped to match the target using a collimator and bolus (compensator) to provide a uniform dose distribution within the tumor (Fig. II-2-2, upper). In 3-dimensional scanning irradiation, the target is divided into slices at right angles to the direction of the beam and irradiated by scanning an unscattered narrow beam in the first slice plane and then in the next slice plane to eventually complete irradiation in the 3-dimensional directions of length, width, and depth over the complex shape of the target (Fig. II-2-2, lower). The 3-dimensional scanning method therefore has better features than the broad beam irradiation method: (1) to be adaptive to deformed targets, (2) to require no bolus or collimator, (3) to provide good control of dose distribution, and (4) to ensure high beam use efficiency.

Three-dimensional scanning for fixed targets was pioneered by the NIRS.[3] It was further refined by the Lawrence Berkeley National Laboratory (LBL, USA),[4] Paul Scherrer Institut (PSI, Switzerland),[5] and Gesellschaft fuer Schwerionenforschung mbH (GSI, Germany),[6] and used in irradiation treatments. In addition, 3-dimensional spot scanning using positron-emitting nuclides ^{11}C or ^{10}C was developed by the NIRS to provide irradiation treatment where the irradiation dose can be precisely verified.[7] However, 3-dimensional scanning for targets moving 3-dimensionally has not yet been achieved because of the great difficulty for dose management. Our study group studied an irradiation method that improves the dose distribution by combining respiration-gated irradiation, in which irradiation is performed only during the respiration phase with the least movement (expiration), and a repainting raster-scanning method, in which provide repeated irradiation. A major problem in this method is the speed of scanning. In the early 3-dimensional scanning method, the beam supply had to be stopped on spot movement or the sojourn time of the spot had to be made so long that the extra dose while the beam spot is moving can be neglected. In other words, it could be applied to treatments with a very low intensity beam. To overcome this problem, we estimated the extra dose, examined the raster scanning method without the beam ON/OFF for each spot, and proposed a high-speed 3-dimensional scanning method in which uniform dose distribution is obtained even when the beam intensity is increased.[8,9] To verify this method, we developed a calculation code optimizing the spot arrangement and weight. We used this to make treatment plans for targets of various shapes and sizes and conducted beam tests. An example of the results of this experiment is shown in Fig. II-2-3. In this experiment, the high-speed scanning method was applied according to the treatment plan for bone and soft tissue tumors conducted in the HIMAC. This verification experiment revealed that an improved dose distribution is obtained even if the scan speed is increased by one order of magnitude or more, and the repainting method can be successfully used in a range of appropriate treatment period of time.

In parallel with the development of the high-speed 3-dimensional scanning method, a computer simulation was performed in order to verify the irradiation method for targets moving in response to respiration (combination of respiration-gated irradiation and repainting method). The results revealed that the dose distribution is degraded with the movement of the target even if respiration-gated irradiation and multiple repainting are utilized, as shown in Fig. II-2-4-a. The major cause of this dose distribution degradation is thought to be the movement of the target position for each slice within the short periods the respiratory gate is on. To overcome this problem, we examined a method to irradiate according to the respiratory movement phase within the respiration gate (phase-control repainting). This method improves the dose distribution by completing the irradiation of 1 slice within the 1-cycle of the respiration gate. We performed a computer simulation to verify this phase control repainting method. The results confirmed that about 8 repaintings gives uniformity of dose distribution in the horizontal and depth directions. It also confirmed that an improved dose distribution is obtained in the simulation using respiratory signals from the patients. Since the slice area varies with slices in this method, beam intensity modulation is required but has already been obtained with the HIMAC synchrotron.

We have already succeeded in the experimental verification of high-speed 3-dimensional scanning for fixed targets using the above method. We will conduct an experiment simulating respiratory movement to further verify the improved performance potential of the respiration-gated 3-dimensional scanning method.

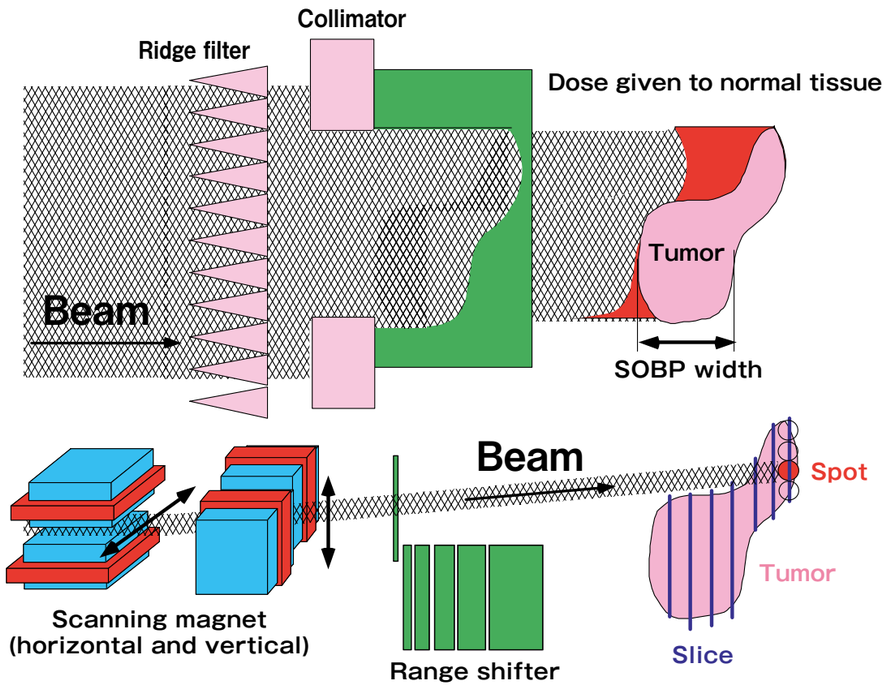


Fig. II-2-2 (Upper) Schematic diagram of the broad beam irradiation system. The beam expanded by the wobbler method in the transverse direction is expanded by the ridge filter in the direction of the beam at the desired depth and is adapted to the shape of the target by the patient collimator and bolus. Since the width of the SOBP is dependent on the maximum thickness of the target, the front side of thin tumors receives an excessive irradiation dose. (Lower) Schematic diagram of a 3-dimensional scanning irradiation system. The spot beam can irradiate the target alone since the tumor position is scanned 3-dimensionally with the scanning magnet and range shifter.

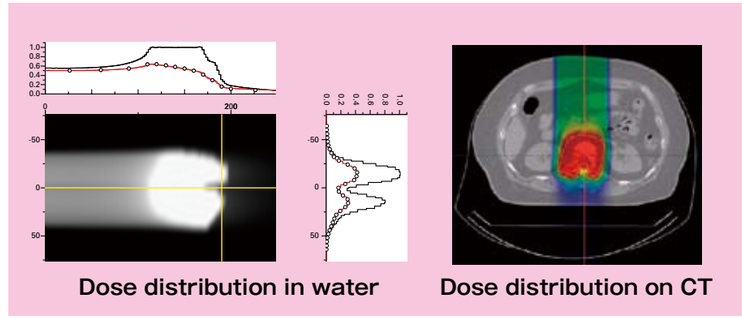


Fig. II-2-3 Dose distribution obtained by the high-speed scanning method
Left, Dose distribution in water. The red solid line represents the physical dose distribution required to obtain the biological dose distribution (black solid line).
Right, Dose distribution reprocessed on the CT image

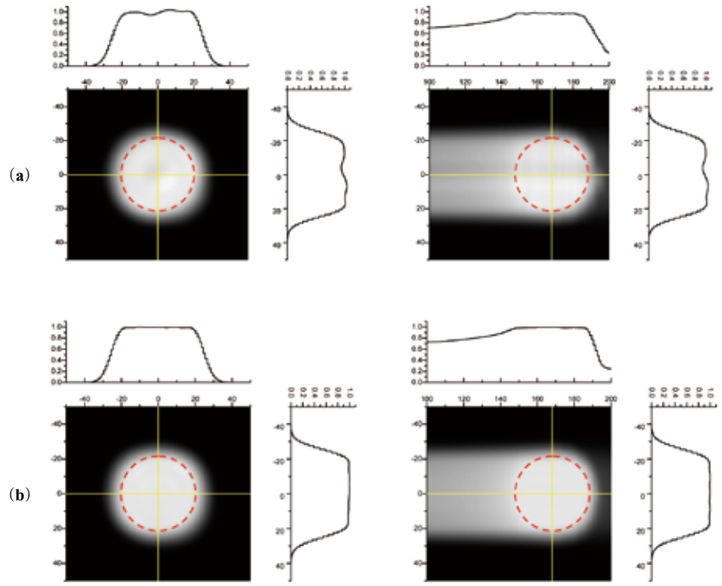


Fig. II-2-4 (a) Respiration-gated and 8-fold repainting, (b) plus respiration phase control Left, Dose distribution in the horizontal direction; right, dose distribution in the direction of the beam depth and horizontal direction; in both (a) and (b)

Development of a carbon beam rotating gantry [10)]

One of the more important results of clinical studies with the HIMAC is the decrease in the number of irradiation fractions. Four-field 1- fraction irradiation for lung cancer achieved a high local control rate although each of the individual doses was decreased. In this 1-fraction irradiation, rapid positioning of the patient is a problem since 4-field (direction) irradiation should be completed within 2 hours. One method of solving this problem is a rotating gantry. The rotating gantry has the advantages of greater ease in treatment planning and patient positioning while improving irradiation precision because of the absence of the organ movement that occurs when the patient is rotated and re-positioned at the fixed irradiation port. It also has the further advantage in that it avoids the need for the patient to maintain an unnatural posture for the long time required in fixed port irradiation as shown in Fig. II-2-5.

However, a rotating gantry for proton beams requires a diameter as large as 10m. The 400MeV/n carbon beam equipment with 3-fold magnetic rigidity is also large and the high total cost is a major disadvantage. Methods for downsizing the rotating gantry may include shortening the irradiation port and increasing the magnetic field of the bending magnet. The latter includes superconducting but there remain many problems to be solved such as quench due to vibration during rotation. Thus, we increased the deflecting magnetic field as much as possible (1.8T) within the range obtainable with ordinary magnets and set the deflection angle at the initial rise at 60 degrees to shorten the axis length as much as possible. We proposed lengthening the irradiation port by using the final bending magnet as a scanning magnet also. We adopted broad beam layer stacking radiotherapy, which is not susceptible to the changes in beam shape due to rotation angle of the gantry, as the field forming method. The concept design is shown in Fig. II-2-6. The total weight is about 300 tons and is half or less than that of the rotating gantry at GSI. According to the structural analysis using the finite-element method, the beam axis displacement in the isocenter is 0.7mm or less and is well within acceptable limits.

If a rotating gantry using the 3-dimensional scanning method can be built, multi-port irradiation can be optimized. Even if important organs exist near the irradiation field, as in cases such as brain tumors, the irradiation field can be formed to avoid them and dose convergence can be further enhanced. In the scanning method, however, a great deal of effort is required for beam adjustment at each angle because the shape and distribution of the beam varies

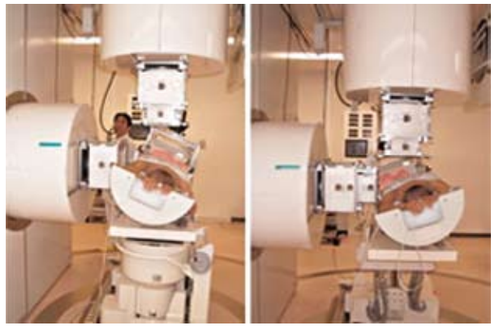


Fig. II-2-5 Positioning for 1-fraction 4-field irradiation. From the website of the NIRS.

with the angle of beam rotation. We thus devised a beam distribution asymmetry compensating method that eliminates rotation angle dependency of beam shape and distribution.[11)] We have tested the design elements of a rotating gantry incorporating 3-dimensional scanning.

Beam control

In the 3-dimensional scanning method, beam control is one of the important subjects for technical development since it uses beams from the accelerator unchanged as described above. Control of the time structure of the beam including beam intensity modulation is especially important for the high-speed scanning and the phase control repainting methods. We have thus vigorously pursued studies on the improvement of the HIMAC synchrotron. For beam extraction in the HIMAC synchrotron, we used and improved the RF-KO method developed at the NIRS[12)] and succeeded in making improvements to the time structure of the beam [13-15)] and to beam intensity modulation.[16)] This is shown in Fig. II-2-7.

In respiration gated 3-dimensional scanning, beam irradiation should be performed only at the time of expiration, when the movement of the target is small, thus extractable time is limited since the synchrotron runs in pattern operation mode. As a result, the irradiation efficiency is very low and the irradiation time may be extremely long. We therefore tried extended flattop operation that uses up the beam after one injection and acceleration. The results of this experiment are shown in Fig. II-2-8. It verified that the combination of this method with the high-speed 3-dimensional scanning method reduced the time of respiration-gated 3-dimensional irradiation from about 2 minutes to 15 seconds.

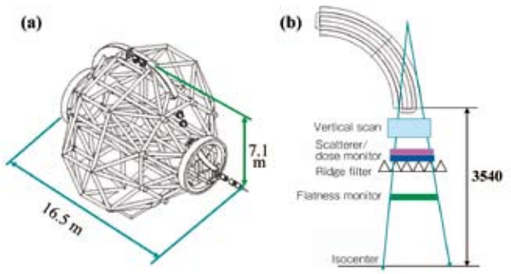


Fig. II-2-6 Conceptual design of a carbon beam rotating gantry. (a) Overall view (b) irradiation port

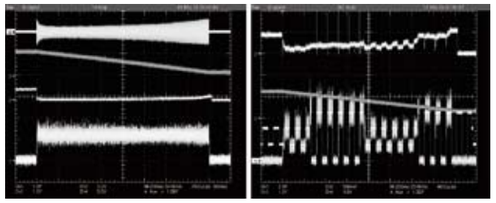
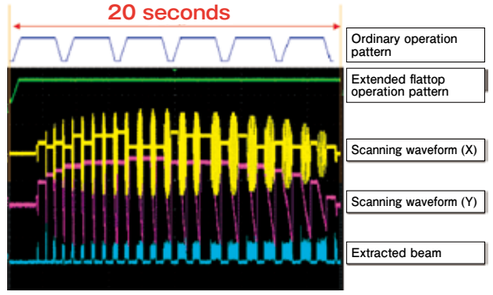


Fig. II-2-7 Time structure of the beam from the HIMAC synchrotron. Left, lowest flow trace, constant intensity beam for 1.6 seconds; right, lowest flow trace,when intensity modulation per 50ms was made in response to intensity command signals

Conclusion

As described above, there are good prospects for the design and construction of a 3-dimensional scanning irradiation system that can be respiration-gated. Our final concept design for the rotating gantry incorporates broad beam layer stacking radiotherapy, and the design of "scanning gantry" using the 3-dimensional scanning method has been started. Our research and development program has resulted in the development of a new patient positioning method, the development of high-precision treatment planning equipment for scanning, and has included a study of a treatment hall design and layout in collaboration with medical staff. We think that the development of a next-generation irradiation system such as we describe is the first step towards achieving an "adaptive irradiation method" which responds to day-by-day changes in the shape and position of the tumor during the treatment in addition to just establish the respiration-gated 3-dimensional scanning irradiation method.

As described above, there are good prospects for the design and construction of a 3-dimensional scanning irradiation system



Beam extraction in the extended flattop operation mode. One injection and acceleration was the equivalent of six ordinary operations of the HIMAC synchrotron.

that can be respiration-gated. Our final concept design for the rotating gantry incorporates broad beam layer stacking radiotherapy, and the design of "scanning gantry" using the 3-dimensional scanning method has been started. Our research and development program has resulted in the development of a new patient positioning method, the development of high-precision treatment planning equipment for scanning, and has included a study of a treatment hall design and layout in collaboration with medical staff. We think that the development of a next-generation irradiation system such as we describe is the first step towards achieving an "adaptive irradiation method" which responds to day-by-day changes in the shape and position of the tumor during the treatment in addition to just establish the respiration-gated 3-dimensional scanning irradiation method.

The success of carbon ion radiotherapy with the HIMAC has had a global impact. Heavy ion radiotherapy facilities are now under construction in Germany and Italy and in France they have decided to introduce carbon ion radiotherapy. In the USA, where some clinicians were critical of heavy ion radiotherapy, it is reported that some facilities started investigating the possibility of introducing carbon ion radiotherapy. Under these circumstances, we think there are good prospects for further advances in heavy ion radiotherapy in Japan and elsewhere that will benefit cancer patients.

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《Ⅲ》Approaches to the Widespread Use of Heavy Ion Radiotherapy

1.Research on the Radiological Protection for Charged Particle Radiotherapy

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Introduction

Since the new therapeutic radiotherapy technologies using proton and carbon ion beams have achieved good therapeutic results, it is expected that use of the therapy will gradually become more widespread. The same safety regulations as in ordinary accelerator facilities have been applied to the radiation protection of staff in medical facilities using charged particles. By considering the framework of radiation protection in the new medical uses of radiation including charged particle radiotherapies, and collecting the data based on the practical dose measurements, the radiation protections on the radiotherapy facilities were evaluated. For the study, the information needed to establish the future concrete structural standards and safety guidelines was accumulated with the cooperation of 6 facilities performing proton or carbon radiotherapies in Japan. The necessity of the matters to be added in the current regulations was also examined.

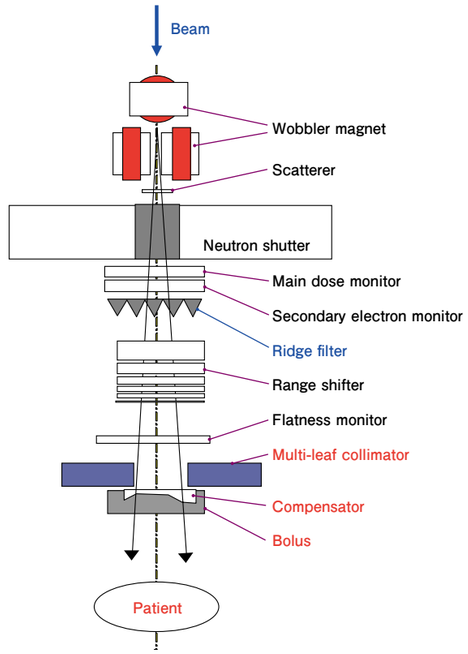

Fig. III-1-1 Structure of the irradiation port
The activated areas which may be touched by medical workers are colored red.

Exposure to medical workers due to the activation of equipment

Leakage radiation from the radiotherapy facility is already regulated and measured and is not a problem. During radiotherapy irradiation, interlock devices prevent all except the patient from entering the irradiation room. The major cause of possible exposure of radiological technologists, physicians, nurses, and the patient's family is induced radioactivity, produced by a nuclear reaction between the irradiated charged particles and the atomic nuclei constituting the equipment and the patient, which remains after finishing the irradiation. We therefore measured the intensity of radiation from this residual radioactivity and evaluated the dose for the radiological technologist, the person who is most likely to be exposed to radiation from this source.

It is expected that the residual radioactivity will be produced in the multi-leaf collimator (some facilities have no multi-leaf collimator but use block collimators, which limit the beam shape very roughly), patient collimator and compensator (both are specific to patients and removed at the end of the irradiation), and the patient's affected region in the order they are seen from the side (upstream) of the accelerator generating the charged particles (see Fig. III-1-1).

These activations were measured with ionization chambers survey meter calibrated in a standard field in accordance with a national standard and traceability within a year (see Fig. III-1-2). The measurements were made with the same protocol in two carbon radiotherapy facilities and three proton radiotherapy facilities.

1) Exposure evaluation

The exposure dose was estimated, assuming that one technologist performs all the work including equipment removal associated with the treatment. The relationship between the work and the dose is as follows: The effective dose due to photons from the multi-leaf collimator is the time integration value of the dose measured at a position 50cm from the irradiation port.

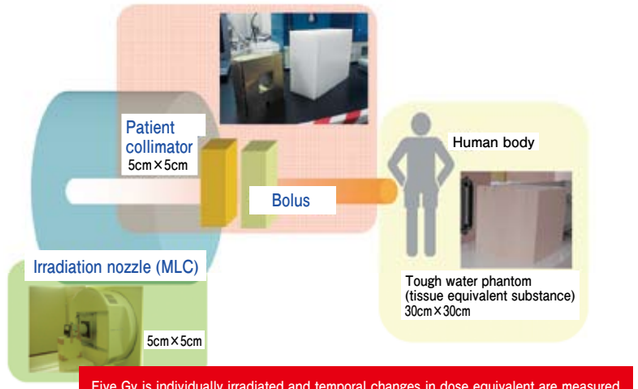

Fig. III-1-2 Irradiation experiment set-up

Mean time required in the NIRS

Work	Time from stopping irradiation to starting the procedure (second)	Time required for the procedure (second)	Distance between the source and the evaluation point					
			Effective dose evaluation (γ)			Skin equivalent dose evaluation (β+γ)		
			MLC	Collimator	Bolus	MLC	Collimator	Bolus
Removal of the patient fixture	25	30	50cm	30cm	30cm	50cm	30cm	30cm
Removal of the patient collimator (placing on the side table)	55	10	50cm	30cm	30cm	1.5cm	0cm	0cm
Removal of the bolus (placing on the side table)	65	10	50cm	30cm	30cm	1.5cm	30cm	0cm
Storage of the bolus (moving to the storage place)	75	15	−*	−*	30cm	−*	−*	0cm
Storage of the patient collimator (moving to the storage place)	90	10	−*	30cm	−*	−*	0cm	−*

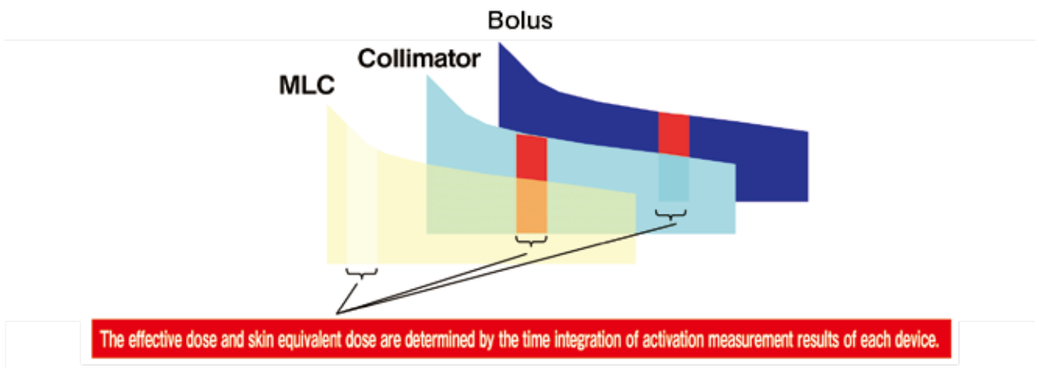

Fig. III-1-3 Work performed by the radiological technologist, time from stopping irradiation to starting the procedures, time required for the work, and distance from the source. The effective dose is measured using the gamma ray dose rate and the skin equivalent dose is determined using the total dose rate of beta and gamma rays. *Dose contribution is ignored because of the long distance.

Similarly, the integration value of the dose rate from the patient collimator and the integration value of the dose rate from the compensator are calculated. The sum of the three integration values is the exposure dose received by the technologist in the removal of the patient immobilization device. Similarly, the exposure doses in the removal of the patient collimator (placing on the side table), removal of the compensator (placing on the side table), storage of the compensator (moving to the storage place), and storage of the patient collimator (moving to the storage place) were determined. The sum of all the doses is the exposure dose of the radiological technologist associated with a one-session irradiation of one patient. To estimate the maximum dose, the time to starting the work was determined with reference to the quickest case and the working time with reference to the longest case. Conditions including

Table III-1-1 Determination of the effective dose and skin equivalent dose of the radiological technologist in a carbon ion radiotherapy

Work	Carbon beam					
	Effective dose (μSv)			Skin equivalent dose (μSv)		
	Facility 1[1)]	Facility 1[2)]	Facility 2	Facility 1[1)]	Facility 1[2)]	Facility 2
Removal of the patient fixture	0.108	0.085	0.054	0.119	0.125	0.099
Removal of the patient collimator (placing on the side table)	0.034	0.018	0.017	0.759	0.252	0.417
Removal of the compensator (placing on the side table)	0.034	0.017	0.017	0.331	0.226	0.136
Storage of the compensator (moving to the storage place)	0.005	0.007	0.006	0.299	0.192	0.111
Storage of the patient collimator (moving to the storage place)	0.023	−	0.007	0.358	−	0.277
Total dose (μSv)	0.203	0.128	0.101	1.866	0.795	1.040
Annual exposure dose (mSv)	1.057	0.665	0.530	9.701	4.132	5.410
3-month exposure dose (mSv)	0.264	0.166	0.133	−	−	−

Note, 1) Low-energy irradiation with a range of about 150mm in water, 2) High-energy irradiation with a range of about 250mm in water

the working time and distance from the source are shown in Fig. III-1-3. Figure III-1-3 shows the values for the irradiation of one patient, and it was assumed that one radiological technologist performs the work shown in Table III-1-1 20 times a day for 260 days per year (65 days per 3 months).

2) Results of the exposure evaluation of the radiological technologist

Table III-1-1 (Facility 1 and 2) shows an example of the results of the exposure evaluation of a radiological technologist working in a carbon ion radiotherapy facility based on the activation measurements made in carbon ion radiotherapy facilities.

The maximum exposure doses in carbon ion radiotherapy were estimated at about 1.06mSv for the effective dose and about 9.70mSv for the skin equivalent dose for low-energy irradiation, and about 0.67mSv for the effective dose and about 4.13mSv for the skin equivalent dose for high-energy irradiation in Facility 1. It was about 0.53mSv for the effective dose and about 5.41mSv for the skin equivalent dose in Facility 2. Even at maximum levels the exposure was 5.5% or less of the current exposure limit.

The dose in proton radiotherapy in Facility 2 was 3.04mSv for the effective dose and about 38.7mSv for the skin dose. In Facility 3 it was about 2.28mSv for the effective dose and about 31.2mSv for the skin dose, and in Facility 4 it was about 5.53mSv for the effective dose and about 73.5mSv for the skin dose. Thus the maximum exposure was 28% or less of the current exposure limit.

The annual effective dose to radiological technologists and physicians in the high-energy medical electron accelerator used in X-ray radiotherapy is negligible at acceleration energies of 10MeV or less but increases rapidly at 10MeV or more. This was evaluated by Almen and Perrin et.al., [1,2] and is summarized in Table III-1-2.

As described above, the effective doses of the radiological technologist were comparable between X-ray radiotherapy using the high-energy medical electron accelerator at 10MeV or more and charged particle radiotherapy. This indicates that there is no need for special regulations, stricter than the conventional regulations currently applied to X-ray radiotherapy, for charged particle therapy facilities.

Table III-1-2 Determination of the effective dose and the skin equivalent dose for a radiological technologist in a high-energy medical electron accelerator

Reporter	Accelerator energy	Trunk	Skin surface
A.Almen (1991) [1)]	13 – 17 MeV	1.0 – 2.8mGy	0.7 – 3.3mGy
B.Perrin (2003) [2)]	18 MeV [Note)]	2.5 mSv	

Note) The effective dose evaluated at 6 MeV is reported to be 2-fold greater.

3) Exposure of the patient's family and effects on the environment

In estimating exposure of the patient's family, it was assumed that the patient's family would be exposed for 2 hours to the integral dose carried by the patient after the patient left the irradiation room 2 minutes after finishing the irradiation. In carbon ion and proton radiotherapies, fractionated irradiation in 1 to 30 sessions is performed on the patient. To determine the maximum possible exposure, the value for 30 sessions was assumed to be the exposure dose per one family member. Based on the activation measurement of tough water phantom simulating the patient, it was estimated at 23.5μSv in Facility 1 (carbon beam) and 128.9μSv for proton and 20.8μSv for carbon in Facility 2.

Given that the time for contact between the family and the patient is limited during the hospitalization of the patient for irradiation, and the fact that the induced radioactivity has a short half-life even, there is almost no increase in the exposure dose of the family if

the visiting time is longer in charged particle radiotherapy. The dose received by the family from the patient is estimated to be a significantly lower than 1mSv/year, which is the dose limit for the general public.

The possibility that radioactivity excreted from the body may be a problem has also been evaluated. The specific radioactivity produced in the patient was about 80Bq/g 5 minutes after irradiation in Facility 1 (carbon beam). The measured half-life of the induced radioactivity is about 13 minutes and the radioactivity is considered to be a mixture of ^{11}C with a half-life of 20 minutes and ^{13}N with a half-life of 10 minutes. The specific radioactivity was 322.8Bq/g after proton irradiation and 45.3Bq/g after carbon beam irradiation 5 minutes after irradiation in Facility 2.

The Law Concerning the Prevention of Radiation Hazards due to Radioisotopes and Others provides for a maximum concentration of 40Bq/cm^3 of ^{11}C in discharged water. Assuming that all the radioactivity is ^{11}C (^{11}C has a longer half-life and is more hazardous than^{13}N), the specific radioactivity of patients is about 1 to 2 times the concentration limit in discharged water after carbon ion radiotherapy and about 8 times after proton radiotherapy. The major route for excretion of this radioactivity is in the urine, however, considering that the water is diluted about 100 times in a toilet and that the radioactivity concentration in discharged water is calculated using the total water discharged from the whole hospital, it appears unnecessary to establish special regulations for charged particle radiotherapy facilities.

International regulations for proton and carbon ion radiotherapies

We investigated the regulations, concepts, and basic documents for safety regulations for charged particles radiotherapies in overseas facilities in operation or under construction. The dose limit and exposure limit in charged particle radiotherapy facilities, like those in experimental facilities using other high-energy particle beams, are subject to the International Commission on Radiological Protection (ICRP) recommendations; in the USA, the National Council on Radiation Protection and Measurements (NCRP) is referred to. There are no regulations specific to charged particle radiotherapy facilities and regulations for X-ray and electron radiotherapies using conventional medical electron accelerators are applied.

Conclusion

We examined the need for radiation protection in charged particle radiotherapy facilities based on a fact-finding survey of foreign countries and the results of measurement experiments in domestic facilities. In overseas facilities, the protection regulations applying to ordinary accelerator facilities are invoked. Evaluation of domestic charged particle radiotherapy facilities, based on measurements of the activation of the therapeutic equipment and patients and the consequent exposure of staff and the patient's family, showed that the exposure dose and the effect on the environment fully satisfied the current regulatory standards. From these results, it is concluded that radiation protection in charged particle radiotherapy facilities has been provided by existing regulation.

This study has investigated the concept of radiological protection in charged particle radiotherapy, summarized opinions of those concerned in facilities in Japan, and collected data on the actual measured radiation exposure dose using a unified method. The result will be necessary for the establishment of future specific safety control guidelines and is expected to contribute to the establishment of the radiological safety system in medical institutions in Japan.

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《Ⅲ》Approaches to the Widespread Use of Heavy Ion Radiotherapy

2.Quality Control in Heavy Ion Radiotherapy

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Tatsuaki Kanai and Shinichi Minohara/ Department of Accelerator and Medical Physics

Due to frequent radiotherapy accidents, the importance of quality control in radiotherapy has been increasingly recognized .[1,2,3] The National Institute of Radiological Sciences (NIRS) established the Radiotherapy Quality Control Section in the Research Center for Charged Particle Therapy in June 2005.

The second mid-term plan of NIRS specifies that the Radiotherapy Quality Control Section develop guidelines and standard methods for the quality control and quality assurance of particle and photon beam therapies. In addition to the routine quality control relating to the radiotherapy, the Section addresses the research and development needed to improve the accuracy of radiotherapy. These include measurement of absorbed dose using a glass dosimeter, development of a calorimeter to determine the absolute absorbed dose of the particle beam, technical examination for establishing the ^{60}Co standard field in terms of absorbed dose to water, and proton dosimetry intercomparison in Japan.

Heavy ion radiotherapy involves various processes and professions in multiple sections using advanced and complicated equipment spread over several sites. The Quality Control Section started to develop the particle therapy quality control system from the view point of human factors, cooperating with the departments concerned.

These activities are expected to influence all radiotherapy facilities in Japan as well as the NIRS. The section also intends to contribute to the field of radiotherapy internationally in cooperation with organizations such as the Forum for Nuclear Cooperation in Asia (FNCA), the International Atomic Energy Agency (IAEA) and the World Health Organization (WHO).

Following the enforcement of the Cancer Control Act in April 2007, social interest in radiotherapy is increasing. The Radiotherapy Quality Control Section tries to meet the social expectations for safe and reliable radiotherapy through these various approaches.

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WHO Radiotherapy Safety Review Meeting (December 2007)

《Ⅲ》Approaches to the Widespread Use of Heavy Ion Radiotherapy

3.Human Resources Development for Heavy Ion Radiotherapy

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Tadashi Kamada/Particle Therapy Research Group

Introduction

Recently, plans for introducing heavy ion radiotherapy facilities in various parts of Japan have been examined, and heavy ion radiotherapy is about to become more widespread. In this respect, the development of the human resources who operate the facilities is one of the greatest problems.

To understand heavy ion irradiation, it is necessary to know the structure of the human body and accurately understand the physical phenomena occurring in the body, such as multiple scattering and nuclear reaction. The biological effectiveness of heavy ions is weak immediately after passing the skin of a body but becomes extremely strong just before stopping, and varies with the depth in a body. To utilize these features to enhance the therapeutic effect and inhibit side-effects, more extensive specialized knowledge is required than for conventional therapeutic radiation such as X-ray and gamma-ray (photon) radiotherapies. Special facilities and equipment, including a high-energy accelerator to produce the charged particle beams, buildings specially constructed for the protection against neutron radiation exposure, more complicated irradiation equipment than for photon irradiation, and the ancillary facilities to operate this equipment are required. Specialist staff who can operate and maintain these facilities are also required.

While various professions, such as radiological oncologists, radiological technologists, and medical physicists are already engaged in cancer treatment with photon beams, additional knowledge specific to heavy ions will be required. In addition, support by staff specializing in the operation and maintenance of new equipment such as the accelerator and the irradiation equipment, and in treatment planning will be indispensable for heavy ion radiotherapy (Fig. III-3-1). However, there is no framework for imparting knowledge of heavy ion radiotherapy in the education system at present. When heavy ion radiotherapy was at the research stage, these human resources developed their knowledge and skills by studying together under the guidance of superior officers and seniors at the study sites. The fact that a considerable number of those now providing treatment in existing charged particle radiotherapy facilities, including proton radiotherapy facilities, are from the NIRS or trained by the NIRS reflects the fact that human resources development has been a kind of apprenticeship. However, when the facilities being planned start to operate, a large number of trained staff will be required in a short period, and a systematic human resources development program different from the conventional one will be required.

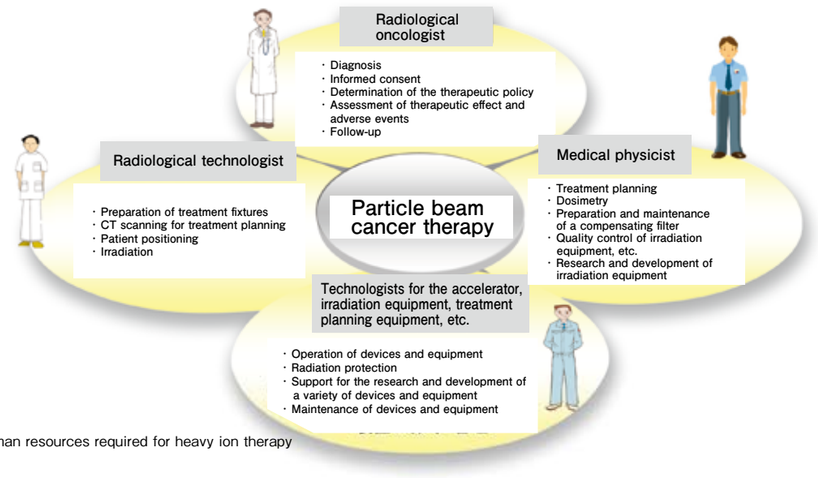

Fig.III-3-1 Human resources required for heavy ion therapy

Previous results

It is reported by experienced persons in Japan that ideal operation of a heavy ion radiotherapy facility requires a staff of about 13 physicians, 3 medical physicists, 10 radiological technologists, and 4 device and equipment technologists. These numbers of staff assume that there is no medical institution nearby and that the facility operates independently. The number of full-time staff may be decreased if the facility cooperates with other institutions such as a neighboring general hospital. The optimal number varies with the target disease and the number of patients treated. Daily improvement in the skill of young members as a result of the guidance given by senior staff in the facility is expected. However, one or more persons should be fully trained as the core staff for each profession before the opening of the facility. This is the same as in proton radiotherapy. If 8 to 10 charged particle radiotherapy facilities are constructed during the next 10 years, at least 40 trained specialists will be required.

The NIRS has actively accepted and fostered the training of physicians and radiological technologists from external institutions such as universities and local governments. In the 20 years of so since charged particle therapy began, 34 former NIRS staff or persons trained by the NIRS have got a job as a member of staff in domestic or foreign charged particle radiotherapy facilities. These consisted of 10 physicians, 15 medical physicists or equivalent, 6 radiological technologists, and 3 device and equipment, including the accelerator, technologists. In addition, since 2001, the NIRS has made a major contribution to the propagation of specialists by accepting 65 trainees including those who are not specified for heavy ion radiotherapy.

To further promote the spread of heavy ion radiotherapy, as part of the second mid-term plan, we have increased our efforts in human resources development for heavy ion radiotherapy since 2006. We especially increased the training of medical physicists, who give physical support and advice in treatment. Because the national qualification of medical physicists is less advanced in Japan than in Europe and North America, there are few professional education systems in schools and the present number of medical physicists is insufficient. In addition, there are few medical physicists engaged in radiotherapy at clinical sites. In these circumstances, we train existing medical physicists in further advanced knowledge of physics and biology. In addition, to foster medical physicist's skilled in charged particle therapy, we are training graduates with science and engineering doctorates. This is done through research and practical work at the heavy ion radiotherapy sites, and the trainees will obtain the qualification of medical physicists, in addition to mastering more specialized knowledge on the physics and biology of heavy ion radiotherapy. Our target is to train 12 persons in the next 5 years.

Future plans

To give assurance that the persons trained have obtained the necessary skills, it is essential that a curriculum giving details of the training program is written so that external persons can understand the program, and it is required to assess the content of the curriculum. Particle beam therapy is at the stage of progressing from research to widespread clinical application worldwide and there is no training system for human resources development specialized in the therapy. The PTCOG (Particle Therapy Co-Operating Group), an academic organization consisting of persons experienced in particle beam therapy, organized a subgroup and has just started exploring the best options for fostering the training of future staff.

In anticipation of these movements, the Ministry of Education, Culture, Sports, Science and Technology started the "Program for the Human Resources Development Relating to Charged Particle Radiotherapy" as a new project for 5 years from FY2007. The purpose of the project is to give on-the-job-training (OJT) to university graduates at practical treatment sites in order to develop core human resources, such as radiation oncologists, medical radiological technologists, and medical physicists, who have the necessary professional knowledge and practical skills.

To conduct this project efficiently throughout Japan, we propose that the 6 particle beam therapy facilities in Japan including the NIRS develop human resources jointly. In developing and promoting the project, we organized a committee consisting of experienced persons from NIRS and other facilities to examine the overall objectives, to design the curriculum, to coordinate communication

Course	Subject	Purpose	Period	Remarks
Basic training	Unlimited	Understanding the characteristics and biology of various cancers (malignant neoplasms) and the various diagnostic and therapeutic methods	1 to 2 weeks	Lectures and observation trips
First term clinical training	Radiotherapy trainee Clinicians in other departments, etc.	Understanding the basic clinical items and radiotherapy equipment, determining the method and indication for charged particle radiotherapy, treatment planning, therapeutic irradiation, and follow-up after the end of treatment	6 months	Clinical training
Second term clinical training	Trainees who have completed the first term clinical course Radiotherapy specialists	Mastering the basic clinical items and practical training administering charged particle radiotherapy	3 months + 3 months	Clinical training
Specialized training	Trainees who have completed the second term clinical training Charged particle radiotherapy specialist	More specialized clinical practice Select the appropriate course, procedures for different organs and diseases, and engage practical experience including, treatment planning and monitoring after treatment.	3 months	Clinical training

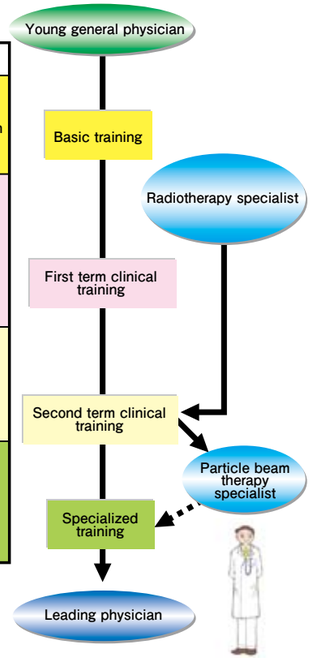

Fig. III-3-2 assumed modularized training courses

between the existing facilities, to evaluate the progress of the project, and to make recommendations on how best to implement the program. It is proposed by the 7 institutions that the facilities cooperate in giving the lectures based on the curriculum, provide OJT in existing facilities, and certify the completion of the course by trainees. Further, it proposed that the Association for Nuclear Technology in Medicine deal with the administration of the project so that this burden does not interfere with the daily treatment of patients in each facility.

One problem with this proposal is that medical staff already working at professional levels is assumed to be a major target for further training and would find it more difficult to commit to several years training than would students. A further factor that might make the training program complicated and inefficient is the prior education and experience levels of those seeking training in charged particle therapy techniques. Trainees may include persons with no experience in radiotherapy to those skilled in ordinary photon therapy. It is therefore planned to construct a system that will allow taking lectures independently by establishing a training program for each profession that is modularized at each level as much as possible. For example, in the case of charged particle radiotherapists, a system is planned in which a young physician with no experience in radiotherapy starts with the basic training course, but a mid-level physician experienced in radiotherapy with photon beams may skip the basic and first term courses and start the second term course, while physicians who have completed a series of training courses and been engaged in charged particle radiotherapy would take specialized training courses for each disease, etc. to become leading physicians as shown in Fig. III-3-2. If such a program can be developed and each course can be taken separately, it will greatly improve the efficiency of training the various professionals required in the future.

To give assurance of the quality of the training, a system is planned in which a certificate is given when a trainee successfully passes an examination after the completion of the prescribed courses in each training program and when it has been confirmed that the trainee has acquired the overall ability to carry out charged particle radiotherapy. It is important that this certification is given according to a standard, nationally unified by a committee. It will be an objective of program developing this training system to cooperate with related societies to make it a socially meaningful qualification.

The NIRS will match its current human resources development plan to this new governmental system, further develop human resources based on the nationally unified standards, and make efforts to foster this training system devised in Japan as an international standard.

《Ⅳ》**Biological Studies of Heavy Ion Radiotherapy**

1.Clinical effect model

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Tadashi Kamada, Particle Therapy Research Group
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Introduction

X-rays widely used for radiotherapy are called low linear energy transfer (LET) radiation and transfer energy weakly and uniformly into cells while heavy ion beams, including carbon beams, are called high LET radiation and transfer energy locally and densely. This difference in the nature of the interactions markedly affects the biological and clinical effects.[1] Thus, it was necessary to establish a clinical effect model for the heavy ion beams before starting heavy ion radiotherapy.

The National Institute of Radiological Sciences (NIRS) had experience in radiotherapy with fast neutrons, a high LET radiation, before beginning carbon ion radiotherapy. Our own clinical effect model, HIMAC model,[2] was established as a hybrid of the clinical experience with fast neutron and biological experiments with heavy ions. Since the inception of carbon ion radiotherapy, NIRS has treated more than 3,100 patients and excellent clinical results have been obtained, but this would not have been achieved without this model.

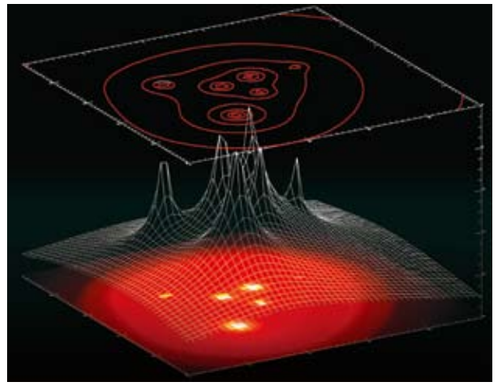

Fig. Ⅳ-1-1 : Dose distributions for the ions of Z = 1～6, E =290MeV/n, injected into water simulating a nucleus of a cell whose size is 7μm (log scale).

In the Hyogo Ion Beam Medical Center, which was the second carbon ion radiotherapy facility in the world following the HIMAC, the HIMAC clinical dose distribution model is used. In Germany, where different clinical effect models are used to perform experimental carbon ion radiotherapy, compatibility with the HIMAC model is being assessed before the carbon ion radiotherapy facility starts providing cancer therapy. The HIMAC model is now established as a standard model for the clinical effects of carbon ion irradiation. In this article, we outline the HIMAC model, describe the verification based on the clinical results, and discuss the future of the clinical effects model based on further studies.

Clinical effect model

When heavy ions used for treatment collide with the atomic nucleus of a substance as they pass through the beam delivery devices and the human body, a nuclear fragmentation reaction that shatters both occurs.[3] Since the spatial energy distribution formed by heavy ions depends on the type of ions and the energy (radiation quality) (Fig. IV-1-1), heavy ions injected into the body of the patient are mixed beams of particles having various biological effects. Handling this variability is an important role of the clinical effects model for heavy ion radiotherapy.

In the HIMAC model, the quality of the mixed beam is expressed using an indicator of dose mean LET, focusing on the dependency of relative biological effectiveness (RBE) on the mean LET value. The dose mean LET is the calculated based on the distance between the interactions, which produces a certain energy transfer. This parameter is known to provide a good indication of biological effect for high LET particles. It can be used to estimate the effect of beams without having to consider the individual particles in the treatment beams injected at a few hundred million particles per second.

The biological effect also depends on the endpoint. Cells cultured from human salivary gland tumor (HSG), which showed moderate response characteristics in an experiment in which various cultured cell lines were irradiated, were selected as the standard cell line expected to give a response to carbon beams typical of tumors. The HSG cells were irradiated with carbon beam, X-ray, helium beam, and neon beam beams of various LETs to parameterize the response characteristics using the LQ model. The spread out Bragg peak (SOBP) used for treatment is designed to be uniform at a survival rate of 10% for HSG in the SOBP based on the tabulated parameters. This level of irradiation corresponds roughly to that in one session of the conventional fractionation.

The standard biological dose for carbon beam was determined by the method above. The clinical dose distribution was determined by aligning the clinical results of fast neutron radiotherapy with the standard biological dose. In the fast neutron clinical study in the NIRS, a clinical RBE value of 3.0 was obtained when 0.9Gy was irradiated in 16 fractions. The RBE of carbon beam varies with LET. The LET of a carbon beam giving a biological effect equivalent to that of a fast neutron beam was determined experimentally, and it was assumed that at this biological neutron-equivalent point the clinical effect is also equivalent to that of fast neutron irradiation, namely the clinical RBE=3.0. All experiments using the 10% survival rate of HSG as the endpoint and the in vivo experiments, such as in mice, showed that the dose mean LET of a carbon beam gives an effect equivalent to that of fast neutron irradiation at about 80 keV/μm. From these results, the dose mean LET of 80keV/μm was determined as the neutron equivalent point.

As an example, the relationships between the physical dose, the biological dose, and the clinical dose when carbon beam irradiation of 2.7GyE is prescribed to a tumor are summarized in Fig. IV-1-2. At the neutron equivalent point (near the end of the range, at the depth of about 150mm) the RBE is 3.0 (as described above) and therefore the physical dose is 2.7/3.0=0.9Gy. The biological RBE in HSG cultures corresponding to this physical dose is 2.0 and the relationships between the physical dose, biological dose, and clinical dose is determined at the neutron equivalent point. The clinical dose distribution was determined by multiplying the biological dose by the ratio of the clinical RBE to the biological RBE at this point (i.e. multiplying by 3.0/2.0=1.5). From ridge filters designed by this method to form SOBP of 2.5 to 150mm in width, the one best matching the thickness of the tumor of individual patients is selected and used for the treatment irradiation.

The main feature of the clinical dose distribution with the HIMAC model is that the RBE is uniquely determined as a function of depth based on the LET dependency and does not depend on other factors such as the tumor site, histological type, oxygenation state, dose, or fractionation. Excluding these factors (the effects of which have not yet been clarified completely) from the design of the clinical dose distribution enabled physical evaluation of the model from the clinical results.

Analysis of clinical results

The validation of the HIMAC model[6] and evaluation of tumor sensitivity and the effect of hypofractionation [5] was based on the clinical results ,tumor control probability (TCP), obtained with the HIMAC. These analyses use the following TCP model [6]:

$$TCP = \prod_i \frac{1}{\sqrt{2\pi\sigma}} \exp\left\{-\frac{(\alpha_i-\alpha)^2}{2\sigma^2}\right\} \cdot \exp\left[-N\exp\left\{-n\alpha_i d\left(1+\frac{d}{\alpha_i+\beta}\right)+\frac{0.693(T-T_k)}{T_p}\right\}\right]$$

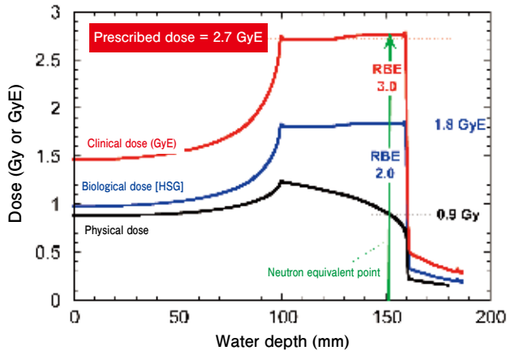

Fig. IV-1-2 Clinical dose distribution (red line), biological dose distribution (blue line), and physical dose distribution (black line) of 290 MeV/n-^{12}C beam used in the HIMAC (SOBP 60mm)

where α, α_i [Gy^{-1}], and β [Gy^{-2}] are primary and secondary coefficients of the LQ model; σ [Gy^{-1}], variance of α; N, number of clonogens in the tumor; n and d [Gy], number of fractions and the physical dose of a single fraction irradiation; and T [day], Tk [day], and Tp [day], number of treatment days, growth delay time, and tumor doubling time.

Fig. IV-1-3 shows a comparison of the local control rates in 18-fraction fractionated irradiation of non-small-cell lung carcinoma (NSCLC) with X-ray and carbon beam irradiation analyzed using this TCP model. The RBE when the TCP was used as the endpoint was 2.3 at the 95% level and was close to the clinical RBE (2.38 at the mid-point of a 60mm SOBP) assumed in the HIMAC model. Considering that a higher response rate is expected for the treatment, the clinical RBE assumed in the HIMAC model appears appropriate. An increase in RBE following an increase in TCP is an important feature of carbon ion radiotherapy; this suggests that local control with X-ray irradiation may be difficult in patients with radiation-resistant cancer whereas the carbon beam may achieve high local control irrespective of individual patients tumor sensitivity. The parameter a representing the tumor sensitivity derived from the clinical results was 0.75, similar to 0.76 measured for HSG cultures, confirming that the sensitivity of HSG cultures is representative of that of tumors.

One of the advantages of carbon ion radiotherapy being clarified by the clinical studies with the HIMAC is the effectiveness of hypofractionation. The first step to be taken when hypofractionation is performed is the selection of the prescribed dose. Although high doses that frequently produce serious side effects are out of question, it does not benefit the patient in terms of local control to start at too low a dose to ensure safety. It is therefore desirable to estimate the local control rate in advance even in a dose escalation study and to start at an appropriate dose.

TCP analysis is very effective in meeting this need. When the clinical results of 18-fraction irradiation for NSCLC were analyzed with the TCP model and the results used to estimate clinical results expected from 1- to 9-fraction irradiation, the actual clinical results were predicted very accurately. Use of the TCP model has been very helpful in determining the single fraction irradiation starting dose after for cases of liver metastasis following colorectal cancer.

Figure IV-1-4 shows a comparison of TCP curves of skull base chordomas, bone and soft tissue sarcomas, rectal cancer, and NSCLC with 16-fraction irradiation. Because 16-fraction irradiation was not performed on NSCLC, results of 18-fraction irradiation were corrected and used. The sensitivity to carbon ion radiotherapy at each tumor site is being gradually clarified. The fact that bone and soft tissue sarcomas, which are generally more resistant to X-ray than NSCLC, were controlled with a low dose of carbon beam irradiation suggests the interesting possibility that there is a clinical effect mechanism specific to carbon beam irradiation.

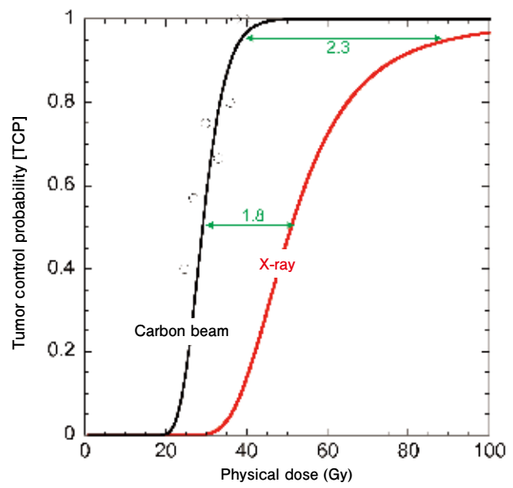

Fig. IV-1-3 TCP of non-small-cell lung carcinoma with 18-fraction irradiation of X-ray and carbon beam

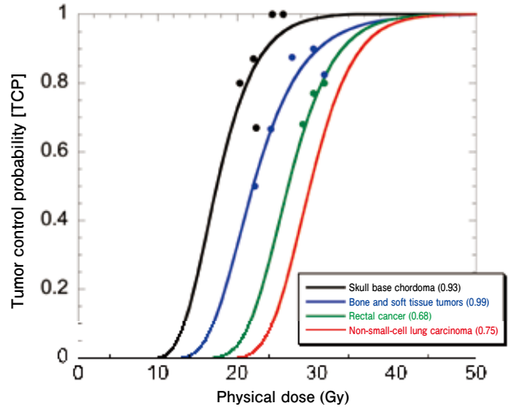

Fig. IV-1-4 Local control rates for skull base chordomas, bone and soft tissue tumors, rectal cancer, and non-small-cell lung carcinomas with 16-fraction irradiation (the value in ( ) is the a value obtained from the TCP model)

The future of clinical effect model studies

As described above, the validity of the HIMAC model using a universal clinical dose was demonstrated from the clinical results and valuable knowledge on the clinical effects has been obtained using this feature. In this section, we will describe two key parameters that may allow improvements to be made to the clinical effect model.

The first key parameter is radiological sensitivity. In the current HIMAC model, radiological sensitivities in all body regions and tissues are represented by the response characteristics of HSG cells, but sensitivities specific to each region are being clarified as shown in Fig. IV-1-4. The prescribed dose is now being adjusted to take into account these differences, but a model design optimized for the sensitivity of each tumor type and body region may further decrease the dose to surrounding normal tissue while maintaining the local control rate for tumors with a sensitivity different from that of HSG cells.

The second key parameter is dose dependency. If the dose dependency of individual tumor types is found, the dose to surrounding normal tissue may also be decreased in the case of hypofractionation. However, in vitro and in vivo biological experiments are difficult to perform for a range of large doses that inactivate all the cells within the tumor using a single irradiation and therefore clinical results are very important in the verification of dose dependency.

The LQ model that is the basis of HIMAC model functions very well but phenomenal. To enhance the predictability of the clinical effect of heavy ion beams, we are conducting a study on the model itself. In one study, we used microdosimetry to measure the energy distribution for high-energy beams of photons and protons, helium, carbon, neon, silicon and iron ions (LET = 0.5-880keV/mm) in a minute space the size of the cell nucleus[7] at various depths in a plastic phantom. Survival curves for HSG cells were also obtained under the same conditions. Then the survival curves were compared with those estimated by a microdosimetric model based on the spectra and the biological parameters for each cell line.

From this year, we have added biological experiments and are conducting a study based on the feedback from the clinical results. It is expected that progress in these studies will contribute to the advancement of charged particle radiotherapy by enabling further optimization of clinical dose distribution and allowing prior estimation of clinical effects when the indications are extended to new tumors or new ion species used for intractable cancer.

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《Ⅳ》Biological Studies of Heavy Ion Radiotherapy

2.Aims of Biological Studies

2-1 Radiation Quality and Biological Effects of Heavy Ion Beams

-LET,RBE,DNA Damage,Damage Repair,and Oxygen Effect-

Yoshiya Furusawa, Leader of the Biological and Physical Study Team,
Heavy-Ion Radiobiology Research Group

More than 10 years have passed since the start of carbon ion radiotherapy, and remarkable results have been achieved in more than 3,100 patients. The therapy has always been based on the biological studies of the effects of heavy ions, and the treatments are still being further developed today. In this article we discuss the present status of biological studies in the Research Center for Charged Particle Therapy. Firstly, we will present the biological properties of heavy ion beams (Furusawa). Secondly, we will discuss the HiCEP method, recently developed by the Center, as the most important analytical method for biological studies (Abe). Thirdly, we will examine the results of studies to enhance the effect of heavy ion beams on cancer cells and reduce the damage to normal cells which progress basic biology to future clinical practice (Okayasu and Anzai). Finally, we introduce our attempts to predict the therapeutic effect and the risk by genetic analysis, to use these predictions to optimize treatment (Imai).

Characteristics of particle beams: LET, RBE, and OER

X-rays, gamma rays, and neutron beams used for cancer therapy have their greatest intensity in a shallow area just under the skin, and the intensity of the beam attenuates with increasing tissue depth (Fig. IV-2-1). In contrast, particle beams such as proton beam and heavy ion beams have a weak intensity near the body surface, but the radiation intensity increases with depth, forming an extremely enhanced Bragg peak at the point where the particles stop and energy transfer is greatest. Imparted energy per unit length of the particle track is called linear energy transfer (LET) and is a parameter determining the quality of radiation. Heavy ion beams are known as high LET radiation (several tens to thousands keV/μm) while X-ray and gamma ray beams provide low LET radiation (a few keV/μm or less). Actual particle track also has an energy transfer distribution in the transverse direction, but the LET is integrated up to infinity in the transverse direction and 3-dimensional structure is not considered. This 3-dimensional structure depends on the type of particles and the passing speed (about 70% of the speed of light at the body surface with the therapeutic carbon beam of the HIMAC). Energy transfer from heavy ion beams damages the DNA of cells, and the type of damage varies with energy transfer density, namely, with LET. Since the type of DNA damage influences the biological effect, the quality of radiation is determined by the LET.

Relative biological effectiveness (RBE) is used as an indicator for the difference of biological effect due to the quality of the radiation. This is a method of expressing the effects of a particle beam required to give the same specified biological effect (e.g. death of 50% of cells), the value is calculated as a ratio to a standard X-ray dose, and this RBE value is usually higher in high LET radiation. RBE depends on LET, but the contribution of the physical 3-dimensional structure is ignored. The degree of LET dependency varies with the bio-indicator chosen (e.g. cell death, mutation and so on) and the type of cells or tissues. In terms of cell death, RBE increases with an increase in LET. It reaches the maximum value at around 150keV/μm, decreases thereafter, falling to a value of 1 near 1,000keV/μm, and is less than 0.1 at 10,000keV/μm or more. Additionally, there is a contribution from the 3- dimensional structure, and the biological effect varies with the type of particles forming the beam even when the beams have the same LET. In particles with an atomic number smaller (proton and helium) than that of carbon used for treatment, the LET when RBE is largest is low but the RBE value itself is large. In contrast, charged particles such as iron have a small maximum RBE, but a large LET at that point. Carbon ions have a different biological effect as a whole

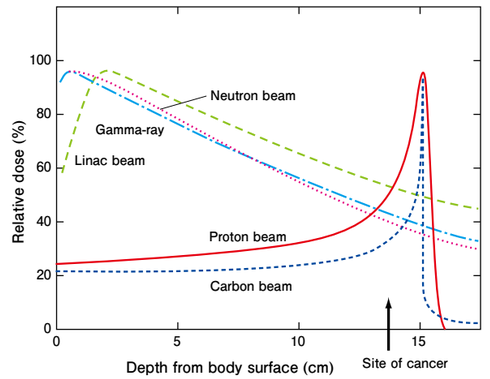

Fig. IV-2-1 Dose distribution of various radiations in the body
The neutron beam and gamma-ray give the maximal dose to tissue immediately after passage into the body, while the proton beam and heavy ion beams give their maximal dose immediately before the particles stop and the dose at the plateau is low. Adjustment of the acceleration energy can alter the depth at which the particles stop as a way of targeting the cancer lesion.

because the beams then contain a mixture of smaller particles by fragmentation of carbon ion when they pass through the body. There is a big difference in RBE with the type of particle, in addition to the difference due to the LET, especially in the range of about several hundreds keV/μm. These variations in the beam used in actual clinical treatments are less problem since they are adjusted to obtain the intended effects before using them by information obtained through biological experiments. However, when new beams are used, expression as a function to estimate the biological effect due to the type of particles and the changes in LET is performed in order to facilitate the estimation of the dose and verification of the results.

The same considerations could apply to the oxygen enhancement ratio (OER). The OER is the rate of the enhancement of the radiation effect in the presence of oxygen. In ordinary organs and tissues, they are fully oxygenated, and the enhanced radiation effect means that only about 1/3 of the dose necessary when oxygen is completely absent is required to provide the same biological effect. Cancer tissues with a poor vascular distribution (and hence low levels of oxygen) are relative insensitive to irradiation and this can lead to the recurrence of the tumor after radiotherapy. In heavy ion radiotherapy, the OER is less near 150keV/μm where the RBE reaches a maximum and cancer cells are more easily killed with a large RBE and a low OER. It was believed that it was unnecessary to consider the modification of the radiation effect by repair of DNA damage or by drugs in high LET radiation. However, it has recently been shown that these effects still exist even with high LET radiation, although to a minor degree. Therefore, it has been suggested that better clinical results will be obtained if these factors are considered in charged particle radiotherapy.

Future particle beam treatments

Recent developments including advanced imaging of cancer tissue by PET or other systems, diagnosis enables cancer tissue to be represented efficiently by combining functional images such as PET and MR with CT to visualize the hypoxic area and then using precisely targeted particle beams to focus the dose on that location.

A further advancement of heavy ion radiotherapy may be the use of radioactive beams (RI beams) (Fig. IV-2-2). RI beams such as ^{9}C emit low energy particles after a delay at the beam stop position at the deeper end of the Bragg peak and the addition of this effect may result in a higher biological effect. A comparison of cell death rates obtained by a ^{9}C beam and an ordinary ^{12}C beam with the same dose distribution revealed that RBE of the ^{9}C beam was the same as that of the ^{12}C beam in the low LET area on the front side of the Bragg peak where no delayed particles were produced, but was about twofold higher in the area where delayed particles were produced. This indicates that a 1.2 to 1.3 times higher therapeutic gain factor will be achieved at the plateau and in the tumor area if a SOBP of 6cm, which is the same as that used currently for treatment, is considered.

Fig. IV-2-2 Short half-life nuclide beam
The ^{12}C beam consisting of six protons and six neutrons is deprived of three neutrons in the passage through the Be block and becomes a ^{9}C beam of six protons and three neutrons. This decays 0.1265 seconds after generation and emits two alpha-rays and one proton beam as delayed particles. This ^{9}C beam stops within the cell near the Bragg peak and exhibits a strong biological effect combining the effect as a primary particle beam with the effect of the delayed particles.

2.Aims of Biological Studies

2-2 HiCEP Method-for medical applications

Masumi Abe
Leader of Transcriptome Research Group

Gene expression profiling analysis is a basic technique in current advanced life science research. The hybridization-based methods including the DNA microarray for measuring gene expression comprehensively, which is widely used throughout the world today, has an inherent problems in sensitivity, reproducibility, and cross-hybridization that are difficult to overcome, even after technical improvement in the methods. We have thus developed a gene expression profiling method, High Coverage gene Expression Profiling (HiCEP), using a different principle.

Background

Characteristics of disorders targeted by medicine

The study of the medicine is sometimes intrinsically more difficult than basic biology. Basic biology was developed based on genetics isolation of mutants causing death, severe dysfunction, and abnormal morphogenesis are key approaches. These extreme traits, however, are rather simplified experimental systems and are more rarely seen in a human population. In contrast to some more simple experimental models, the human population is a very complicated and non-uniform population where extreme mutations leading to death or other severe abnormalities have already largely been eliminated during evolution. In other words, a genetic disease of concern to medicine usually exhibits a minor abnormality initially. However, very small changes that lead gradually to large changes in health can be a major problem and detection at an early stage is important in diagnosis. Cancer is an example that is often closely associated with the aging of stem cells, can lead to fatal diseases that develop with aging. Studies on the mechanism of aging have just started and its understanding at the molecular level is a subject for future research.

In the clinical settings, best detectors detect minor abnormality; physicians observe carefully and systematize common abnormalities. For example, in former times public health records were a treasury of systematized phenomena based on an enormous screening program, and they provided not mechanism studies but very important information for society. If this advanced monitoring system is combined with a high-precision high-throughput molecular analysis system, the data from clinical settings must be cutting-edge of basic research. It is difficult to use existing screening methods that have been developed for basic genetic research for medical studies without changing the methods to overcome inadequate sensitivity, reproducibility and specificity. We have developed the HiCEP analysis system to overcome these problems.

Features and problems of the HiCEP method

In the HiCEP method, transcripts are distinguished by the presence or absence of the restriction enzyme recognition sites and the length of fragments produced by digestion. Synthetic adaptors are ligated to both sides of an enormous number of fragments digested by the restriction enzymes (30,000 to 40,000 fragments/cell) (hereinafter referred to as HiCEP substrates), and PCR is run with a pair of primers annealing on the adaptors. This enables amplification while the quantitative ratio among HiCEP substrates is maintained very accurately. It is a feature of HiCEP that it can analyze the several tens of thousands of amplified HiCEP substrates individually, enabling us to perform a highly quantitative analysis on 30,000 to 40,000 transcripts/reactions. Features of the HiCEP method are shown in Table IV-2-1. A major feature is that it does not require any sequence information in advance and therefore can be used for any eukaryote including those for which there is little or no accumulated genetic information. The ability to detect unknown transcripts and to observe low abundance transcripts accurately can be an advantage in medical research in future.

However, there is a problem in that it is necessary to determine the sequence of the peaks after HiCEP analysis since the genes from which specific peaks are derived are not known in advance, but it is noteworthy that it is not necessarily required to determine the sequences of the peaks of interest for diagnosis and monitoring.

2-3 Biological Effect of Heavy Ion Irradiation and Cancer Cell-Specific Radio-Sensitization

Ryuichi Okayasu
Leader of the Heavy-Ion Radiobiology Research Group

Table Ⅳ-2-1

	Conventional method (microarray, DNA chip)		HiCEP
Detection sensitivity	Copies/cell (expression change)	> 10 to 200 (2-fold or higher)	1 to 2 (1.2-fold or higher)
Coverage rate		10 to 98% known gene	70 to 80% known gene + unknown gene + non-coding transcripts
Reproducibility		Problem in detection of low-abundance transcripts	Good
Experimental procedure		Simple	Complicated
Others		Cloning is un necessary after analysis. Sequence information is required in advance. Limited (EST analysis is advanced) species	Cloning is necessary after analysis Sequence information is unnecessary. All eukaryotes can be analyzed.

Approaches to studying the effect mechanisms of heavy ion beams

Because of the high sensitivity, the HiCEP method has successfully detected minor changes in gene expression in situations where detection was previously impossible. Fujimori et al. identified the genes in human fibroblasts whose expression was changed by irradiation with 10mGy. Tabata et al. identified the genes whose expression was induced by the irradiation embryo with 5mGy, and Ando et al. identified the genes whose expression was induced by a magnetic field.

A study of the mechanism of the effect of heavy ion beams using HiCEP has already been started by the Study Team for the Cellular Molecular Mechanism, Heavy-Ion Radiobiology, Research Center for Charged Particle Therapy. In this study, normal human fibroblasts (HFLIII) were irradiated with a high LET carbon beam from the HIMAC and the changes in the gene expression at 2, 4, and 8 hours were analyzed using HiCEP. A comparison of the expression profiles of 15,000 gene transcripts revealed that the expression of about 40 genes increased by 3-fold or higher within 4 hours after a carbon beam irradiation dose of 2Gy (about 70keV/mm). Most of these were known DNA damage response genes, such as CDKN1A, MDM2, and Gadd45 a, controlled by the p53 transcription factor, but the genes whose expression was changed included some genes in which such a response had not been reported. We are comparing the changes in expression after irradiation with X-rays (2Gy) and a low LET carbon beam (13keV/mm) and exploring the biomolecules specifically associated with irradiation with the high LET particle beam used for treatment.

The HiCEP method opens up several future prospects, including the advancement of treatment based on the clarification of the mechanism of the effect of heavy ion beams, and the ability to focus on genes providing useful information including cancer candidates. It is anticipated that the acute sensitivity of the method will lead to future advancements in diagnosis and the assessment of therapeutic effects; for this it is not necessary to determine the relationship of genes only to recognize adverse and advantageous changes.

The advent of the HiCEP method is like the advent of a microscope for observing transcriptome. Furthermore, the shift from the preexisting method to HiCEP is like the shift from a traditional TV to a high-definition TV. We anticipate that some day we can often hear conversations such as 'I checked the patient with HiCEP, then I found that. . .' in the clinical settings.

Characteristics of the biological effects of heavy ion beams

Heavy ion beam irradiation has an advantage to focus the dose on the cells of a solid tumor. This advantage is due to the formation of a Bragg peak at the point where the charged particle beam stops. Heavy ion beams are found to differ biologically from gamma-rays in quality. Unlike X-rays or gamma-rays, which are known as low LET (linear energy transfer) radiations, heavy ion beams with high LET reduce the ability of the cells to repair the irradiation damage and exhibit a high biological effect such as increased cell death rates. DNA double strand breaks (DSB) are the most important form of damage caused by ionized radiation. If this is not correctly repaired, many severe biological effects will result. Fig. IV-2-3 shows an example of the degree to which DNA DSB are repaired in prostate cancer cells after irradiation with X-rays or the carbon ion beams used in the NIRS. When the initial level of DNA DSB was set at 100 %, the DSB produced in X-ray treated cells were repaired considerably faster than in carbon beam irradiated cells (in this figure, the final damage rate is nearly 0 %), but the repair of DSB in cells after carbon beam irradiation was markedly inhibited. The survival rate of the cancer cells after irradiation (dose, 4Gy) is affected greatly, and more cell deaths were observed after carbon ion irradiation than with X-ray irradiation (Fig. IV-2-3, right). This is one of the biological mechanisms explaining why charged particle therapy is more effective.

When DNA DSB is induced in cells by irradiation, the repair mechanism is immediately initiated . Two major repair systems are known to be involved. One is non-homologous end joining (NHEJ) and the other is homologous recombination repair (HRR). Many of the proteins involved in these repair systems are being identified. We have recently shown that the behavior of these proteins after heavy ion beam irradiation differs greatly from that after X-ray irradiation. Specifically, among the proteins associated with NHEJ type repair, the kinetics of phosphorylation and dephosphorylation of protein DNA-PKcs is considerably delayed after irradiation with charged particles (Okayasu et al. Radiat. Res. 165, 59-67, 2006). Phosphorylation of this protein can be observed with a fluorescence microscope using phospho-specific antibodies. One example is shown in Fig. IV-2-4. Studies with these phosphorylation antibodies will play an important role in future DNA repair studies, especially those after heavy ion irradiation.

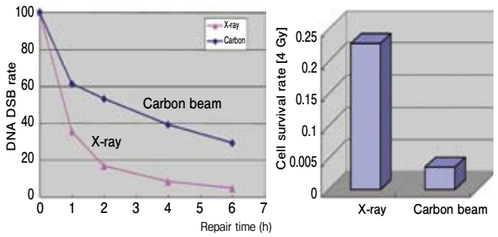

Fig. Ⅳ-2-3 Comparison of the DNA DSB repair (left) and cell survival rates (right) after irradiation of prostate cancer cells (DU145) with x-ray and carbon beams (70keV/μm)

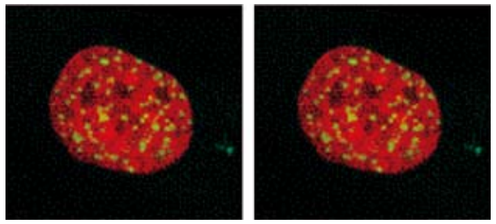

Fig. Ⅳ-2-4 Fluorescent antibody staining of DNA-PKcs phosphorylases one hour after irradiation of 180BR human cells with 2 Gy of X-ray (left) and carbon beam (right)

Radio-sensitizers that specifically sensitize cancer cells

If cancer cells can be preferentially sensitized prior to radiotherapy with treatments that have little or no effect on normal tissue, more effective radiotherapy for cancer will be developed. This would be in addition to the advantages of heavy ion beams already discussed. Based on this concept, we have conducted a study on radiosensitizers specific to certain cancer cells jointly with the Ibaraki Prefectural University of Health Sciences. The results showed that an inhibitor of heat shock protein Hsp90, sensitized cancer cells but scarcely affected normal cells. Fig. IV-2-5 shows the radiation survival rate of cells when the Hsp90 inhibitor,17-allylamino-17-demethoxygeldanamycin (17AAG) was used. As shown in this figure, the rate of cell death increased after the irradiation of X-rays in two types of cancer cells due to the effect of the sensitizer but no sensitization was observed in normal cells (Noguchi et al. Biochem. Biophys. Res. Commun. 351, 658-63 2006). This indicates that 17AAG induces radiosensitization specific to certain cancer cells.

To investigate the cause of this specific radiosensitization, we conducted various experiments. The results showed that the repair of DNA DSB was inhibited in sensitized cancer cells after the administration of 17AAG. This was done using a method of analyzing the broken DNA strands using gel electrophoresis and is shown in Fig. IV-2-6. In contrast DNA repair was scarcely

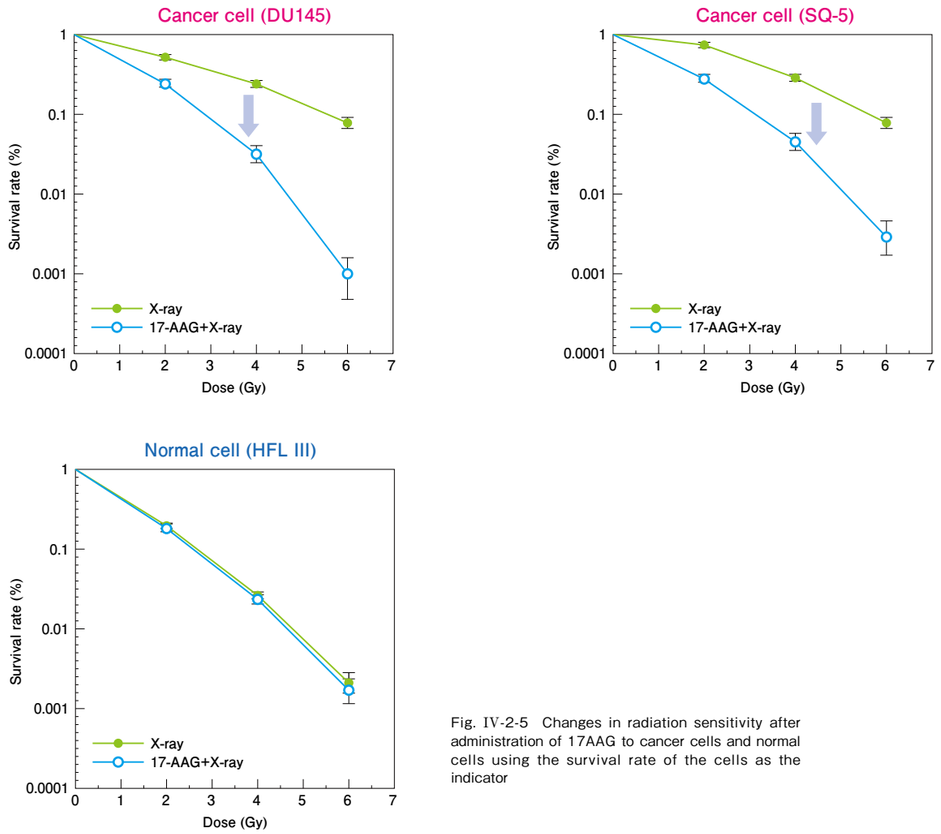

Fig. IV-2-5 Changes in radiation sensitivity after administration of 17AAG to cancer cells and normal cells using the survival rate of the cells as the indicator

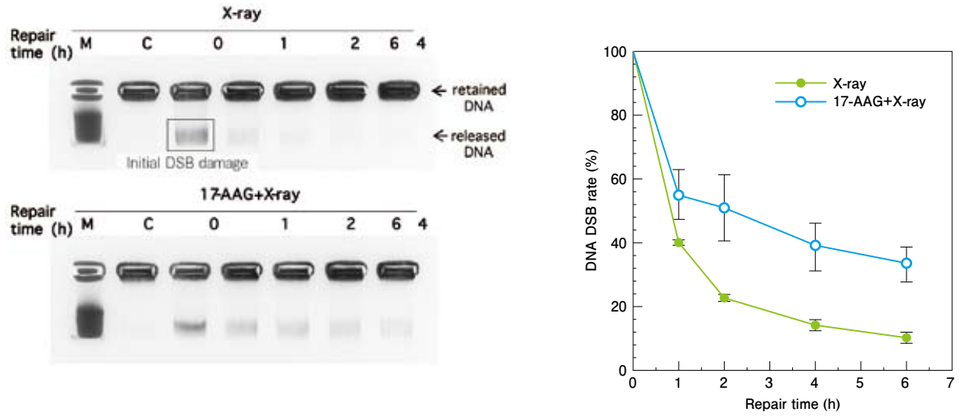

Fig. IV-2-6 Comparison of DNA DSB repair in prostate cancer cells after irradiation with or without 17AAG (left, photograph of DNA gel; right, repair kinetics after image analysis)

affected in normal cells (Noguchi et al. Biochem.Biophys. Res. Commun. 351, 658-63 2006). We demonstrated that this repair inhibition is due to the effect on the homologous recombinational repair (HRR) system of two main DSB repair systems. In addition, an in vivo animal experiment using a mouse model revealed that the combination of 17AAG and X-ray markedly inhibited tumor growth when compared with radiation or drug treatment alone. These results indicate that an Hsp90 inhibitor has great potential as a radiosensitizer for certain cancer cells. Recent experiments showed that 17AAG also acts as an effective sensitizer when combined with heavy ion beam irradiation. This mechanism is now being explored at the molecular level and future clinical application is expected.

Other prospects

Recently, it was found that when cells were irradiated with particle beams from the horizontal direction instead of the vertical direction and observed the irradiation track could be visualized (Fig. IV-2-7) an immuno-staining method. Using this method, the important DSB repair process after irradiation can be directly observed at the intracellular molecular level. We would like to lead the biological studies on heavy ion beams in the world by applying these recent assay systems.

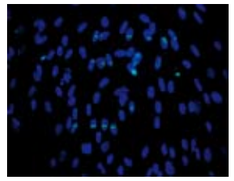

Fig. IV-2-7 Example of the use of γH2AX as a DSB marker after horizontal irradiation of normal human cells with a carbon beam (290 MeV/n) (Kato and Okayasu, unpublished data)

《Ⅳ》**Biological Studies of Heavy Ion Radiotherapy**

2.Aims of Biological Studies

2-4 Radiological Protection of Normal Tissue by Drugs

Kazunori Anzai
Team Leader of Radiation Modifier Team, Heavy-Ion Radiobiology Research Group

The major problem in tumor treatment by radiation is how to prevent radiation damage in nearby normal tissue while increasing the dose to tumor tissue. This problem may be approached from various angles. Our team's approach is to protect normal tissue from radiation damage with drugs (chemicals).

Since the discovery of radiation, studies on how to decrease the adverse effects of radiation have been conducted, and research on radiation protectors has a long history. Extensive screening studies on a series of compounds with the thiol-containing cysteamine as the basic skeleton were conducted in the USA and amifostine (WR-2721) was developed but has not been widely used in clinical practice as a radiation protector because its side effects are not negligible.

In pursuit of protectors with fewer side effects, low-molecular-weight compounds having a structure other than aminothiols and compounds derived from biogenic (natural) substances have been studied, and this trend has recently accelerated. This increased interest arises from the recent demonstration of the importance of free radicals and reactive oxygen species, produced in the body by various factors, in contributing to the etiology of many diseases. As a result there has been vigorous research seeking drugs that protect against free radicals.

Using the ESR spin trapping method, we demonstrated that heavy ions produce more free radicals in the low LET area on the entrance side, where damage to normal tissue may occur, than expected.[1] Thus we considered the possibility that anti-oxidant compounds which protect against free radicals might also have a protective effect in charged particle beam irradiation. We therefore conducted studies seeking compounds having radiation protection activity but few side effects from among the antioxidant compounds. Examples of compounds whose radiation protection activity was found in vivo are shown in Fig. IV-2-8.

Nitroxyl radical has a stable radical structure, exhibits superoxide dismutase activity, and reacts with other free radical species. We found that MC-PROXYL and HM-PROXYL, which can pass through the blood-brain barrier and distribute in the brain, can provide effective radiation protection.[2] The radiation protective effect of another nitroxyl radical, TEMPOL, was investigated in detail by Mitchell et al. of the NIH, and a phase II study was conducted on the prevention of hair loss in radiotherapy in the head.[3]

In seeking compounds with potential as radiation protectors it is most efficient to screen drugs already developed and approved for clinical use and which have few side effects. We investigated the radiation protection activity of edaravone (trade name, Radicut), the only drug with free radical scavenging as a mechanism of action, and found marked radiation protection activity in mice.[4] To obtain this activity, a much higher concentration than that used clinically for the treatment of cerebral infarction as a brain protector is required, and it may be difficult to use this drug as a radiation protector in clinical practice without modification.

In view of the potential side effects, it may be wise to search for radiation protectors amongst natural or biogenic substances. A search of the antioxidant vitamins and their derivatives revealed that vitamin E derivatives TMG and γ-TDMG have a radiation protection activity.[5] A very interesting point in the action of these compounds is that they have a strong activity even when administered after radiation exposure, whereas the compounds discussed above must be administered before irradiation to have any effect. In this respect, these compounds may be good targets for studies on the protection of normal tissues in radiotherapy and for use after radiation accidents. Amongst biogenic substances, we found that α-lipoic acid, which exists in the body as a coenzyme of mitochondrial enzymes, prevents oxidative stress and memory dysfunction in brain after irradiation.[6] Along with the spin probe, α-lipoic acid is an interesting compound in that it can pass through the blood-brain barrier to have a radiation protective effect.

We will examine whether the series of compound described here are effective in protecting against high LET heavy ion beams and aim to clarify the mechanism of action and to develop new compounds.

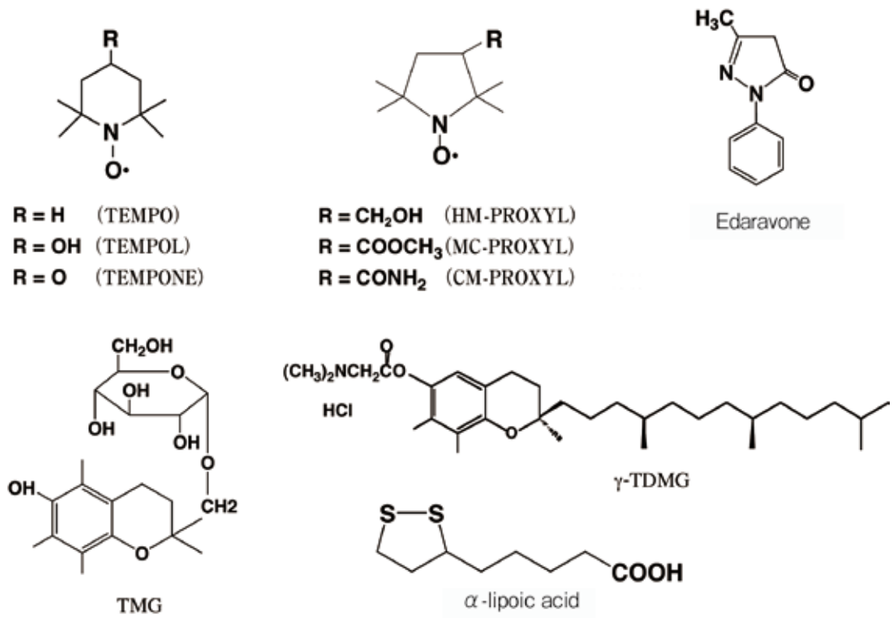

Fig. IV-2-8 Compounds with in vivo radiation protection activity

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《Ⅳ》**Biological Studies of Heavy Ion Radiotherapy**

2.Aims of Biological Studies

2-5 Prediction of the Effects of Heavy Ion Radiotherapy and the Risk of Metastases by Gene analysis

Takashi Imai, Mayumi Iwakawa, Takashi Moritake, Kaori Imadome, Miyako Nakawatari, Minako Sakai, Etsuko Nakamura, Kazunori Nojiri, Tomoaki Tamaki, and Mitsuru Yanagisawa

RadGenomics Research Group

Introduction

Because of the favorable dose distribution, heavy ion radiotherapy shows a high local control rate for cancers. However, some types of cancer are still resistant to heavy ions and show intractable properties. In addition, there is an issue of how metastasis can be inhibited. If the differences in the resistance and sensitivity to heavy ions of the tumor and the surrounding normal tissue in each patient are clarified and the risk of metastasis can be predicted, heavy ion radiotherapy will be utilized more effectively. We have been analyzing polymorphic markers for providing an indicator of radiation sensitivity in individual patients. In addition, we have started to investigate the genome structure and gene expression profiles of tumors that showed resistance to heavy ion radiotherapy, photon therapy, or chemoradiotherapy. Furthermore, we have investigated tumors with metastasis at both the RNA and protein expression levels to isolate effective prognosis markers. In this article, we introduce our recent research aimed as clarifying the mechanism of the therapeutic effects using mainly a microarray technique to follow the dynamics of gene expression in the cancer after irradiation (Fig. IV-2-9).

Expression Analysis of Cervical Tumors

Gene expression profiles of the biopsy specimens were obtained from 63 patients with cervical cancer, before and during fractionated radiotherapy. The microarray system used here was the CodeLink Human Whole Genome Bioarray equipped with 44K probes.

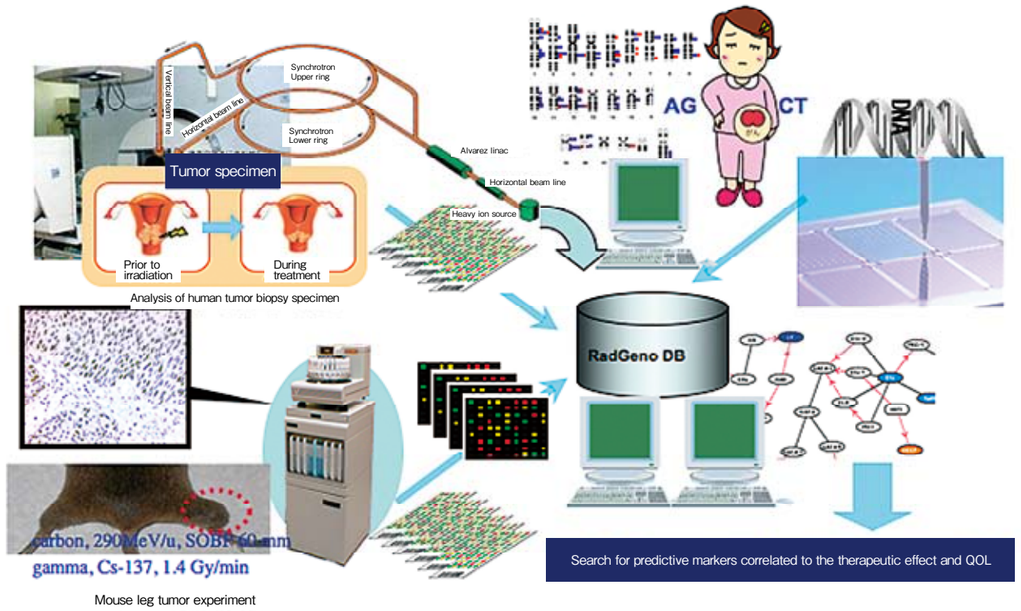

Fig. Ⅳ-2-9 Search for biomarkers correlated to the therapeutic effect and QOL by integrated genome analysis

The gene expression analysis of tumors irradiated by carbon beam showed induction of the genes relating to the TNF-mediated cell death pathway and alternations in the expression of the extra-cellular matrix proteins. For example, expression of CD44 was suppressed in squamous cell carcinoma but induced in adenocarcinoma after carbon beam therapy, suggesting that the control mechanism of gene expression varies depending on pathological types of the tumor. Similar findings were previously obtained in gene expression profiles of the tumors treated by chemoradiotherapy. Such molecules may be clinically important in relation to recurrence of the disease. Because the current number of the tumors analyzed by the gene expression profiling method was still small and because the pathological diagnoses of samples were diversified, we should analyze more samples after accumulation of more cases.

Expression Analysis of Carbon Ion Irradiation Murine Tumors as a Model

We examined gene expression changes after carbon ion irradiation (290MeV/n, SOBP 6cm middle, 50kev/μm) with doses of 5, 10, and 30Gy in six mouse tumors (NR-S1, NFSa, MMCa, SCCVII, #8520, and Mca#4) transplanted into the hind legs of C3H/HeNrs mice, using the CodeLink Mouse Whole Genome Bioarrays at 6 hours, 12 hours, 1 day, and 3 days after irradiation. Gamma rays of 30, 50, and 70Gy were used as a reference beam.

The therapeutic gain factor was determined from the tumor growth delay curve after irradiation. The genes whose expression was changed were subjected to quantitative RT-PCR experiments and a protein expression analysis. The tumors were also examined histopathologically.

The tumor growth delay assay and the gene expression profiling indicated that the pathological types of tumor affected their radiation sensitivity more than the types of irradiation. Many of the genes whose expression was changed by 1.5-fold or higher at 6 hours after carbon beam irradiation were related to cell cycle regulation, and the expression of most of them was suppressed. This suppression was also shown in the samples taken 5 days after irradiation. There were some genes whose expression was increased. Many of these were classified into immune responses including cytokines. Immediately after irradiation with carbon ions, the microscopic effect on the tumors was almost the same as after irradiation with gamma- rays. After a day, the cells showed pyknosis, karyorrhexis and slight swelling of nuclei and cytoplasm. After 3 days, marked infiltration of small round cells was observed, and many arrested cells in the interphase of the cell cycle were noted. A change in the expression of genes specific to regrowing of tumors was also observed. Among them, we found molecules whose expression was increased only in radioresistant tumors. The relationship between these gene expressions and neovascularization is under investigation.

Conclusion

We have analyzed the changes in the gene expression profiles of the biopsy specimens obtained from patients with cervical cancer, before and during fractionated radiotherapy. We have also used mouse tumor models differing in radiation sensitivity as a system for the functional analysis of molecules relevant to the prediction of therapeutic effect and metastasis. Furthermore, we have analyzed the copy number variation of DNA sequences in the tumor genome in both humans and mice to investigate what causes the characteristic gene expression in the tumors. We think it important for the biomedical studies on heavy ion beams to integrate these data with the genetic characteristics of individuals as polymorphic data and to utilize the characteristics of individual patients and individual tumors in planning and performing treatment of cancers.

Special issue Up-to-date results of heavy ion therapy - present status and the future -

V. Present Status and Future Plans for Research Projects

Takeshi Murakami/Technical Management Section (Program Coordination Group), Department of Accelerator and Medical Physics
Kiyomi Kasai/Development and Differentiation Study Team, Radiation Effect Mechanism Study Group, Research Center for Radiation Protection
Toshiaki Kokubo/Laboratory Animal Sciences Section, Department of Technical Support and Development, Fundamental Technology Center
Satoshi Kai/Accelerator Engineering Corporation

Introduction

Clinical studies and cancer treatments using Heavy Ion Medical Accelerator in Chiba (HIMAC) are usually performed from 7 a.m. to 7 p.m. on weekdays. During nights and weekends, studies in other basic science fields using heavy ions from HIMAC are performed. This framework is called the Research Project with Heavy Ions at NIRS-HIMAC (hereinafter referred to as the research project).

Status of HIMAC as an accelerator

What position does HIMAC hold among particle accelerators in the world? Is it a rare facility or a common facility from the viewpoint of basic science?

HIMAC has the capability to accelerate heavy ions up to several hundreds of MeV per nucleon. Accelerators are commonly used in the fields of high-energy physics and nuclear physics. The handbook on accelerator facilities throughout the world, recently compiled by the International Union of Pure and Applied Physics (IUPAP), lists about 90 accelerator facilities, but only 3 facilities including the HIMAC can provide heavy ions of several 100MeV per nucleon. This means that HIMAC is a rare research facility.

Many researchers in the fields other than medicine in and outside the NIRS expressed strong interest for applying high energy beams from HIMAC. Thus, the research project was established to make the facility available to researchers in basic science during the times when HIMAC was not used for treatments.

History and management system of the research project

The research project started in October 1994, a few months after the start of clinical studies with HIMAC.

Before the research project began, a management policy was determined in NIRS. This is summarized in the three main principles as follows: (1) the major purpose of the HIMAC is cancer therapy, (2) the fields of study for the research project should be as wide as possible to utilize the facility efficiently, and (3) the procedure for evaluating proposals should be transparent.

Proposals for the research project are submitted twice a year. The proposals are reviewed in the "Program Advisory Committee (PAC)" of the "Steering Committee for the Research Project with Heavy Ions at NIRS-HIMAC." Most of the members of these committees are external researchers to assure the transparency of the procedure.

It is mandatory to submit a report summarizing progress of the study at the end of every fiscal year, and the progress is presented orally at a meeting. The PAC evaluates these reports and gives advice.

Although the process of "evaluation" is in common usage today, it is remarkable that a system including this concept was created 14 years ago.

Present status of the research project

The proposals are divided into three categories for convenience: treatment and diagnosis, biology, and physics and engineering. The treatment and diagnosis group mainly covers the analysis of the results of heavy ion radiotherapy, development of therapeutic methods and tools, and the research and development of diagnostic methods. The treatment of patients is included in clinical studies and is therefore excluded from the research project. The biology group includes projects for the irradiation of cells and animals, and all the other irradiation experiments are classified into the physics and engineering group.

Figure V-1 shows the number of projects from 1994, when the research project first started. This shows that about 120 to 140 projects have been conducted each year since around 1997.

The beam time supplied to the research project is shown in Fig. V-2.

These values are comparable to those in other facilities dedicated to physics. Since HIMAC has two synchrotron rings and beams from the injector can be used directly, beams can be simultaneously supplied for three independent studies. Multiple irradiations run in parallel, and beam times are calculated independently.

Although the carbon ion is frequently used in biology experiments, the need for other ions has increased. In physics and engineering studies, many types of beams from proton to Xe are used.

The published papers or presented talks in 2005 are summarized as follows.

In 2006, about 520 scientists from outside the NIRS were registered as the collaborative researchers and about 110 NIRS staff members joined the research project. This suggests that good cooperation and collaboration exists.

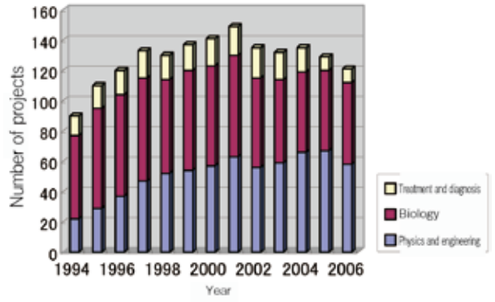

Fig. V-1 Number of the research project studies with the HIMAC

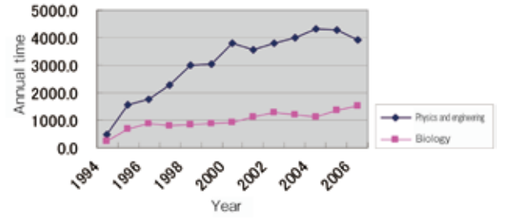

Fig. V-2 Total machine time in the research project studies with the HIMAC

Year	Original article	Proceedings	Oral presentation	Others
2006	72	53	245	72

(Note) Original articles include those accepted and in print but do not include those in submission. The numbers are being calculated and are published as a quick report.

Research using high-energy heavy ion beams

Some of the early studies conducted and the characteristics of high-energy heavy ion beams are described below. Since it is impossible to introduce all the studies conducted because they are very diversified, see the annual reports for details (contact: Research Project Promotion Room).

(1) Quite new types of beams

When the high-energy heavy ion beam enters a substance, it collides with the atoms and atomic nuclei constituting the substance and either becomes extinct (Fig. V-3) or generates new radiation. In physics, the rate of this extinction and generation is called, "cross section" and it serves as the most basic quantity for all the studies. As stated at the beginning of this article, the number of facilities that can provide high-energy charged particle beams in the world is limited. When HIMAC was constructed, there were very few reliable data on the cross section and, initially, acquisition of these basic data were our new study subject.

The cross section of generating of neutrons as secondary particles is the most basic parameter required when designing radiation shielding for an accelerator facility. When HIMAC was constructed, this value had to be estimated based on calculation. The values of the cross section of the generation of neutrons obtained at HIMAC are now available as basic data for the shielding designs for the various accelerator facilities.

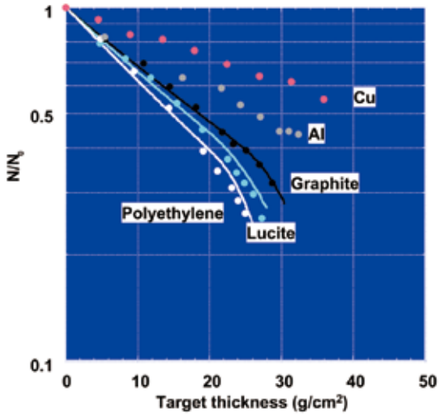

Fig. V-3 Attenuation of 400-MeV/n carbon ions in substances
(provided by Fukumura of the NIRS)

(2) Large LET of the beam

As is well known, the LET value of a carbon ions is larger than that of an X-ray and changes along the track of the ion. Large RBE values, which are a major advantage of heavy ion radiotherapy, are dependent on large LET values. Studies of the differences in the biological effect between carbon beams and X-rays were not only the basic studies required for optimizing treatment but were also a major topic in early research project, attracting much interest from those involved in the biological field. The response of organisms varies greatly between the cellular level, tissue level, and individual level, and depends largely on the environment pertaining at their location. Elucidation of the biological effect is thus being considered very important in studies at HIMAC.

In investigating the physical aspects of the carbon ions, the necessity for a new detector was recognized. Because the LET value is large and varies greatly with depth in the tissue, the conventional detector was found to have an inadequate dynamic range and was unsuitable for use in measuring the spatial dose distribution. To overcome these problems, various proposals including the application of a new principle and the modification of the conventional detector have been presented and are being tested.

(3) Long range of the beam

A long range allows observation of the inside of a large object. One of the applications of this characteristic is heavy ion computed tomography (CT). While the conventional CT measures the absorption of X-rays, heavy ion CT measures the energy loss, a different physical quantity. This is like a photograph taken under the illumination of an entirely different color. Although at the present stage of development it is inferior to conventional CT in spatial resolution, it may be put into practical use in the not-too-distant future, including applications other than medical science, as well.

The long range is optimal for simulating cosmic rays. These days, when plans for space stations and exploration of the planet Mercury are hot topics, a considerable number of studies using HIMAC as a means for accurately estimating the effect of cosmic rays have been completed or are underway.

(4) New types of physical phenomena

One of the attractions of a new type of beams for physics studies is that new phenomena can be observed. For example, it is indispensable in understanding the physics of creating an atomic nucleus not naturally existing in the world and in exploring its basic properties such as the size, shape, and magnetic dipole moment. Such measurements have already been made on several unstable nuclei with HIMAC. There are a very large number of candidate nuclides to be investigated and further interesting results will be produced.

Heavy ions that enter a substance usually collide with atomic nuclei of the substance and some of them are lost. However, if the target is a crystal, under specific conditions the particle beam may pass through the regularly arranged atoms without colliding with each other, like water flowing through a pipe (Fig. V-4). To observe this phenomenon, however, beams of extremely high quality such as those with a spreading angle of 0.02 degree or less are required. There are no accelerators other than the HIMAC that can provide such high-quality, high-energy heavy-ion beams. Excitation and de-excitation using this phenomenon are also observed and this research field is almost exclusively carried out at HIMAC.

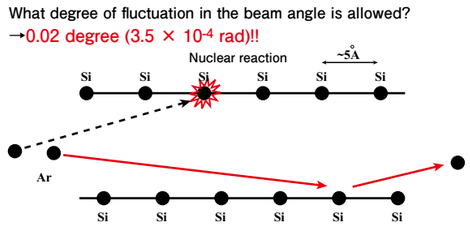

Fig. V-4 An Ar ion is injected into a Si crystal. When a high-energy ion is injected along the direction of the crystal, it can pass through the crystal without nuclear reaction!
(provided by Azuma of the Tokyo Metropolitan University)

Future research project

There is no question that biological studies and improvements in radiation detection methods relevant to medical science will be vigorously pursued. Here we look at the possibility of a new study that has been rarely conducted with HIMAC.

One possibility is to applying the long range to improve the quality of a large object or create a substance having a new function. For example, the degree of the cross-linking of high polymers induced by radiation depends on the LET of the radiation. If the change in LET along the beam is applied and the injection position and the range are controlled, it will be possible to process the substance to have different 3-dimensional properties. The possibility of an application that controls the macro properties of a normally uniform solid substance by using heavy ion beams to create a single or periodic defect in the object may be further examined.

Medical accelerators can supply about 10^9 particles per second, in general weak beam intensity. However, implantation at a concentration of about one ppb (1/1 billion) may be possible in an actual irradiation time. While the present implantation is limited to near the surface, implantation at deep sites, mixing of multiple types of ions, or the formation of a layered structure will be possible if high-energy heavy ion beams are used.

High-energy beams are expected to play a role in the mutagenesis of plants, and have already been the subject of preliminary studies. Because of the high energy, seeds, rootstocks can be irradiated in a whole body level.

Improvement in accelerators may also have a great impact. In principle, beams are emitted from the synchrotron in pulses. It will be possible to make a complete DC beam after currently planned modifications to the accelerator are completed. Such beams can then be used to accurately observe the dose rate dependency of the biological effect, for example.

Knowledge and skills, and time for preparation of the experiment is significant. We have established a support system that allows researchers in other fields to use HIMAC. This is reflected in the fact that more than 80% of the projects undertaken at HIMAC were by researchers, not from areas using accelerators conventionally. There may be many potential users of high-energy heavy ion beams other than the current users. It is necessary to vigorously foster contact with scientists in new fields and to further develop the support systems available to cooperating scientists.

Special issue Up-to-date results of heavy ion therapy - present status and the future -

Impressions of PTCOG 46

Hideo Tatsuzaki, Diagnosis Section, Department of Radiation Emergency Medicine, Research Center for Radiation Emergency Medicine, and Research Center Hospital for Charged Particle Therapy (concurrent post)

Takashi Fujita, Promotion for Carbon Therapy Section, Research Center for Charged Particle Therapy

Introduction

We had an opportunity to attend the 46th meeting of the Particle Therapy Co-Operative Group (PTCOG) held in Zibo, Shandong Province, China from May 18 to 23, 2007.

The host for the meeting was Dr. Jiamin Li of the Wanjie Proton Therapy Center (WPTC). The meeting was composed of two parts: The Educational Workshop was held in the first half of the meeting from May 18 to 20 and the General Meeting was held in the latter half from May 21 to 23. In this period, May 20 and 21, committees such as the Steering Committee also met. The meeting was sponsored by the People's Government of Shandong Province and the Chinese Medical Society. The transportation of foreign participants by bus was guided by a police car, with traffic restriction. (Fig. 1).

Dr. Hirohiko Tsujii, Director of the Research Center for Charged Particle Therapy, NIRS was elected as the chairman of the PTCOG for 3 years from 2007, and this was the first PTCOG meeting held under his chairmanship. Thus, he acted as the chairman of the Steering Committee, etc. A total of ten members of the NIRS and several former members participated in the meeting.

Zibo Wanjie Hospital Proton Therapy Center

We introduce briefly the Zibo Wanjie Hospital Proton Therapy Center that hosted the meeting. This hospital is a private institution and is a part of a private company Wanjie Group Co., Ltd. Wanjie Group, a company focusing on the textile industry, owns the Wanjie

Fig. 1 Police car guiding a bus transporting participants

Fig. 4 Rotating gantry treatment room

Fig.2 New ward of the Zibo Wanjie Hospital

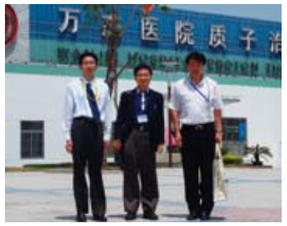

Fig. 3 Front of the Zibo Wanjie Hospital Proton Therapy Center

Fig. 5 The opening ceremony of the Educational Workshop

International Hotel, where the Educational Workshop was held, and is associated with the adjacent university. The Zibo Wanjie Hospital is an affiliated hospital of this company, which was established in 1992 and has 500 beds (Fig. 2). The Zibo Wanjie Hospital Proton Therapy Center is the first charged particle radiotherapy facility in China, and is located in Boshan District, Zibo, Shandong Province, about 500km southeast of Beijing (Fig. 3). It has the IBA 230MeV cyclotron as an accelerator, one horizontal irradiation room, and one gantry room (Fig. 4).

The main staff includes 7 radiation oncologists, 11 medical physicists, and 13 technologists. Clinical treatment started in December 2004 and 339 patients had been treated by March 2007.

Educational Workshop

The Educational Workshop was held at the Wanjie International Hotel from May 18 to 20. This was a course for explaining the basics of charged particle radiotherapy to new or potential users. At the opening ceremony, Ms. Duan Liwu, the deputy mayor of Zibo, Mr. Sun Qiyu, the President of the Wanjie Group, and Dr. Alejandro Mazal of the Curie Institute in France, the chairman of training for the PTCOG Educational Workshop, gave addresses (Fig. 5). Numerous TV cameras and still cameras were set up (Fig. 6), and many advertising balloons celebrating this meeting were put up near the hotel, suggesting that this PTCOG meeting was a big event locally.

There were 180 participants, and 25 lecturers gave presentations covering basic physics and engineering, biology, and clinical aspects of each organ system. After dinner, a demonstration of dosimetry and treatment planning system was provided. Drs. Junetsu Mizoe, Hirotoshi Kato and Hirohiko Tsujii from the NIRS gave lectures.

Fig.6 Dr. Kato interviewed by a TV reporter after his lecture

Fig.7 People's Hall of the Luzhong Hotel where the General Meeting was held

Committees

A preparatory meeting of the Publication Sub-committee was held at Wanjie International Hotel on May 20. Ideas for publication activities and the method of selecting the chairman and members of the Sub-committee were discussed under the chairmanship of Dr. Tsujii, and proposed to the Steering Committee.

Prior to the General Meeting, in the early morning on May 21, the Steering Committee was held at the Zibo Hotel. The Committee was led by Chairman Dr. Tsujii, Former Chairman Dr. Smith, and Secretary Dr. Jermann. The most important item at this committee meeting was that the Statutes of the PTCOG, which had not previously been stipulated, were adopted and the PTCOG was to be registered as a non-profit organization in Switzerland. The financial issues, travel fellowship to help fellows attending the meeting, Educational Workshop policy, and the establishment of the Publication Sub-committee were also discussed. The meeting venue of PTCOG49 (2010) was decided by vote among three candidate sites. The meeting in 2010 would be held in Japan, with co-organization by Gunma University and NIRS. In addition, Dr. Akine, a former professor of the University of Tsukuba, was elected as an honorary member.

General meeting

In the latter half of the conference, the General meeting was started in the hall of the Luzhong Hotel (Fig. 7) from 9 a.m. on May 21, by opening remarks of Chairman Dr. Tsujii (Fig. 8). The guests of honor, including the Deputy Head of the Shandong Province, the Mayor of Zibo, the President of the Chinese Medical Society, and the President of the Wanjie Group attended the opening ceremony. The ceremony was carried out with great splendor with the Deputy Mayor of Zibo as a master of ceremonies, and with about 700 participants attending. The authors felt the creative vigor of China. Subsequently, registered members of various facilities

Fig.8 Dr. Tsujii, the chairman of the PTCOG gave an address at the opening ceremony

in the world gave about 60 oral presentations covering their study results and the state of their facilities and held discussions, for 3 days. Drs. Hirohiko Tsujii ,Takeshi Yanagi from NIRS and Satoru Yamada from Gunma University gave lectures entitled "13-year experience of carbon ion radiotherapy at NIRS", "Carbon ion radiotherapy for bone and soft tissues sarcomas of the head and neck" and "New carbon therapy project at Gunma University Heavy-Ion Medical Center" respectively. In parallel with the oral presentation, 47 poster presentations were made. Dr. Yoshiyuki Iwata. NIRS, presented a poster, "Development of a compact injector for heavy-ion medical accelerators." These presentations allowed us to discuss the development of charged particle radiotherapy in Japan over the past 13 years, to present detailed clinical results, and to talk about the development of compact equipment as "clinical" equipment. Among presentations by foreign participants, the ongoing construction of proton radiotherapy facilities and development of spot scanning irradiation were impressive for us.

Appearance of the streets

After lunch on May 19, during the Educational Workshop, Mr. Zong Shujie, a staff member of the Wangie Hospital (as a volunteer) guided Dr. Yanagi and the authors to the hospital and around the hotel. He enthusiastically explained the facilities of the hospital, origin of the shape of a pond in the garden of the hotel, etc. in English. His parents house is located near the old family home of Chu-ko Kung-ming, famous for Sanguozhi (Three Kingdom Saga), and we enjoyed his amiable companionship.

On the evening of May 22, during the General meeting, Dr. Yanagi and I (Fujita) went into the streets for a meal and to buy souvenirs. We walked along the street of "delicious food", found a homely restaurant at the edge of the town, and had a chance to experience popular Chinese food different from the continuously served smorgasbord in the hotel. We ordered two dishes each and drank a beer at a total cost of 17 yuan (280 yen) for two of us. When we wrote "delicious" in kanji (Chinese characters) on a piece of paper and handed it to the waitresses as we left, they sent us off with a nice smile. The street visit made us feel friendly towards China, where our feelings can be communicated with kanji even if we cannot speak Chinese.

随想
occasinal

Rainier III, Prince of Monaco and the International Atomic Energy Agency

Ryushi Ichikawa

A few days after the death of Pope John Paul II last July, the death of Rainier III, Prince of Monaco was reported. Rainier III, well known in Japan for his marriage with Grace Kelly, the famous Hollywood actress, had participated in our research field related to marine radioactivity over a long period.

The prince first became involved in marine radioactivity in 1959, when a major symposium on the disposal of radioactive wastes in the ocean, sponsored by the International Atomic Energy Agency (IAEA), was held at the Oceanographic Museum in Monaco. At that time, the IAEA earnestly addressed the problem of low-level radioactive wastes, produced through the peaceful uses of atomic energy, being disposed in the ocean. The government of Monaco assisted the IAEA in holding the international symposium of marine radioactivity and Rainier III invited the symposium participants to the garden of the royal palace where a grand party attended by Princess Grace was held. This occurred soon after their marriage in 1956.

In 1961, two years after the symposium, the IAEA International Laboratory of Marine Radioactivity was established as a part of the Oceanographic Museum in Monaco. This was a co-operative project between the government of Monaco, the IAEA, and the French Research Institute for Exploitation of the Sea (IFREMER). The IFREMER was involved because the Oceanographic Museum was affiliated with the French institute. The IAEA International Laboratory of Marine Radioactivity has since moved to new premises and been renamed the IAEA Marine Environment Laboratory; it now undertakes research on other ocean contaminants as well as radioactive waste.

In the Oceanographic Museum, there are aquariums and water tanks containing fish, etc. that attract sightseers. On the second floor, there is a display room containing fishing equipment and tools collected by Prince Albert I, which are very interesting to Japanese visitors.

Dr. Rinnosuke Fukai left Japan to take up an appointment at the International Laboratory of Marine Radioactivity, where he was engaged in the study of marine radioactivity for an extended period. His particular focus was plutonium in sea water. Many young Japanese researchers visited this institute and benefited from his assistance. Dr. Fukai worked at this institute until he retired, at which point he was the head of the institute. He worked originally at the Tokai Regional Fisheries Research Laboratory (currently the Central Research Institute, National Research Center of Fisheries Science).

When Rainier III was young, mid-1960s, he visited Vienna incognito with his wife, Princess Grace. They came to Grinzing, where wine bars are concentrated, a famous place in the northern area of Vienna, and enjoyed a night out. Dr. Kempo Tsukamoto, Director of the NIRS at that time, his son-in-law Tetsuya, his wife Ruriko, and I were in one of the bars when it was visited by Prince Rainer III and Princess Grace. We thus had an opportunity to see Rainier III and his wife dancing elegantly from a short distance.

In the autumn of 1982, about 15 years later, a car driven by Princess Grace crashed over a precipice on the road from Nice to Monaco and she was killed.

It was the happiest time for Rainier III when they visited Vienna incognito. In later years of Prince Rainier III, Prince Albert, his oldest son, often deputized for him. When the IAEA Marine Environment Laboratory moved to new premises, Prince Albert attended the opening ceremony with Dr. Blix, Director-General of the IAEA.

ICHIKAWA RYUSHI
(former vice-president, NIRS)

Editor's note

The muggy season has arrived but dew on the hydrangea flowers still appears cool. When we see these dew covered flowers in the shade on the way to the office, we feel grateful, even in this humid season. The newly designed blue cover page looks cool like a dewy hydrangea and is delightful.

The cover page of this July issue, published in early summer, is in a cool marine blue color and incorporates an up-to-date medical image in blue. This is a CT image that demonstrates the successful treatment with carbon ion radiotherapy of an intractable malignant tumor, which had not been cured by other therapies. This is a special issue focusing on carbon ion radiotherapy, which has attracted attention from throughout the world after 13 years of clinical studies.

Our institute celebrated the 50th anniversary of its foundation this year. The studies of heavy ion radiotherapy for intractable cancer have progressed through the steps of planning, implementation, and the accumulation of results over the past quarter-century. This special issue provides an overview of the studies from the past, the present, and the future. We will be pleased if the many current researchers and staff, our predecessors who spent a major part of their lives in radiation research, and the general public learn of and appreciate the significance of the activities of the NIRS. (by HK)

Announcement of the next issue

Special issue "Technological development and safety in NIRS"

Yoshikazu Nishimura,	Director of the Fundamental Technology Center
Hidehito Nakamura,	Department of Technical Support and Development
Hisashi Kitamura,	Department of Technical Support and Development
Toshiaki Kokubo,	Department of Technical Support and Development
Masanori Okamoto,	Department of Technical Support and Development
Teruaki Konishi,	Department of Technical Support and Development
Noriyoshi Suya,	Department of Technical Support and Development
Yosuke Ichikawa,	Department of Safety and Facility Management
Takeshi Maeda,	Department of Technical Support and Development
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