

**Carbon-ion Radiotherapy—Basic and Clinical Studies—
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Abstract

Radiotherapy using charged and/or high-LET particles has a long history, starting with proton beams. *In vitro* data clarify that RBE (Relative Biological Effectiveness) increases with LET up to approximately 150 keV/μm for carbon-12 and neon-20 ions. *In vivo* studies show that tumor control probabilities after single doses of gamma rays shift to higher doses when tumors were irradiated with 5-fractionated doses, while such a shift is not observed for carbon ions, and that tumor reoxygenation is accelerated after carbon ions compared to γ-rays. The RBE for tumor control is greater than that for the skin response when fibrosarcoma and skin of mice are irradiated with 3-5 dose fractions of 290 MeV/u carbon ions. Experimental results of secondary tumors induced by carbon ions are included. Clinical results for various malignancies are also presented here.

1. Introduction

Radiotherapy using charged and/or high-LET particles has a long history, starting with proton beams. Ion beams “heavier” than protons, such as carbon, neon, silicon and argon were tried in Phase I clinical trials, but the only heavy ion beams currently in use for radiotherapy are carbon. The radiation quality of particle beams is different from conventional photons, and therefore biological effects of high-LET irradiation have drawn the scientific interests of quite a few scientists in both basic and clinical fields. After the closure of the Bevalac accelerator complex in Berkeley, California that was used for the heavier- ion trials, hadrontherapy with carbon beams was undertaken both in Japan and in Germany to continue the research.

Full-scale clinical studies with carbon ion therapy started in 1994 at the NIRS (National Institute of Radiological Sciences) in Chiba, Japan using the HIMAC (Heavy-ion Medical Accelerator in Chiba) synchrotron, and clinical trials with carbon at the GSI (Helmholtzzentrum für Schwerionenforschung GmbH) in Darmstadt, Germany followed. Until 2009, almost 4000 patients have been treated by NIRS and 400 patients by GSI with extremely good results.

Encouraged by these results, other facilities also started carbon-ion therapy or construction of

particle accelerators for radiotherapy; Hyogo Ion Beam Medical Center, Japan and the Institute of Modern Physics, China started carbon-ion therapy in 2002 and 2006, respectively. The Heidelberg Ion Beam Therapy Center (HIT) in Germany will start proton/carbon ion therapy in 2010 while the following four synchrotrons are currently under construction: Gunma University Heavy Ion Medical Center at Maebashi in Japan, CNAO (Italian hadrontherapy center) at Pavia in Italy, and two new facilities in Germany, the Kooperative Ionen Therapie Zentrum at Marburg and NRock North European Radiooncological Center at Kiel.

2. Experimental studies of carbon-ion beams

In vitro data

The relationship between LET and RBE has been extensively studied using *in vitro* cultured cell lines (Furusawa 2000). Figure 1 shows RBE values at a 10% survival fraction for human salivary gland tumor cells (HSG) after single irradiation with helium-3, carbon-12 or neon-20. RBE increases with LET up to approximately 150 keV/ μm for carbon-12 and neon-20 ions. Helium ions show a more rapid increase of RBE with increasing LET than other ions. The oxygen enhancement ratio (OER) for cell kill is approximately 3 for photons, and is reduced when LET increases (Fig.2). OER becomes small when LET increases to 60 keV/ μm and approaches unity at 500 keV/ μm . With increasing LET, helium ions again show a more rapid decrease of OER than heavier ions.

Fig.1

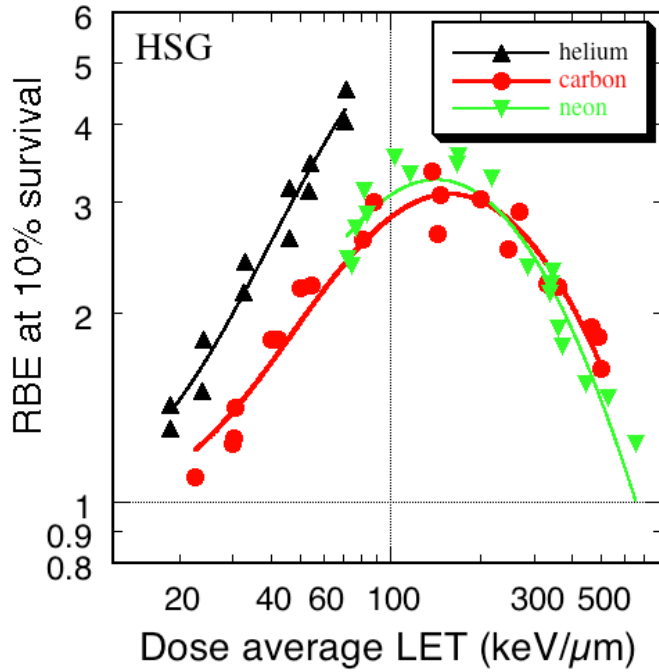
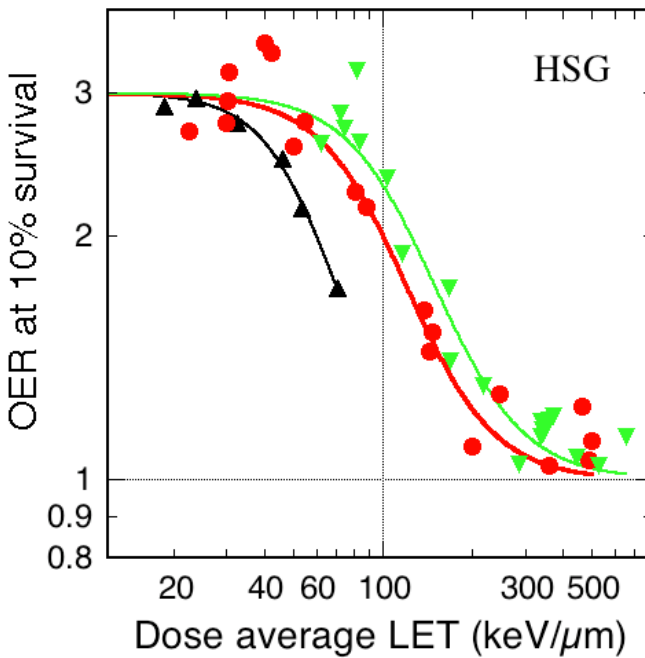


Fig.2



Cytogenetic damage after carbon-ion beams has been studied with primary cultures of human cells (Suzuki 2006). Six primary culture biopsies were obtained from 6 patients with carcinoma of the cervix before starting radiotherapy, and cells at passage 4 were irradiated *in vitro* with X rays

[specify energy] or carbon ions. A good correlation between cell killing and excess chromatin fragments (using the premature chromosome condensation technique) was observed for the 6 different cell cultures (Fig.3)

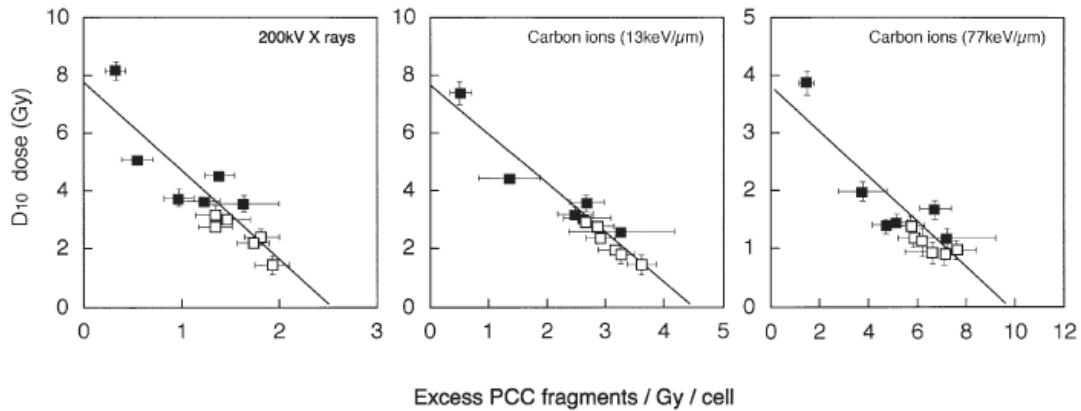
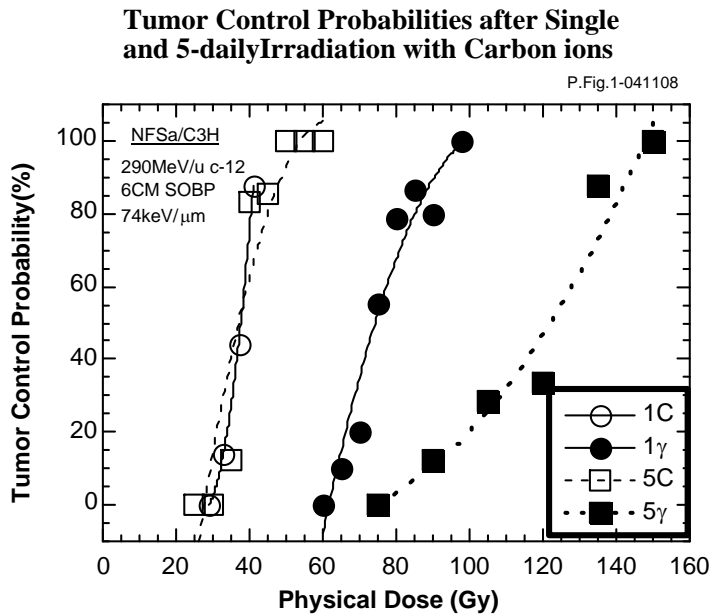


Fig.3

In vivo data

Tumor control probabilities (TCP) after single and fractionated irradiation with carbon ions were studied for a murine transplantable tumor (Fig.4) (Ando, unpublished data). TCP after single doses of gamma rays shift to higher doses when tumors were irradiated with 5-fractionated doses, while such shift is not observed for carbon ions. This observation has led to hypofractionation of carbon radiotherapy with fewer treatments delivered over a short time course (Miyamoto T 2007).

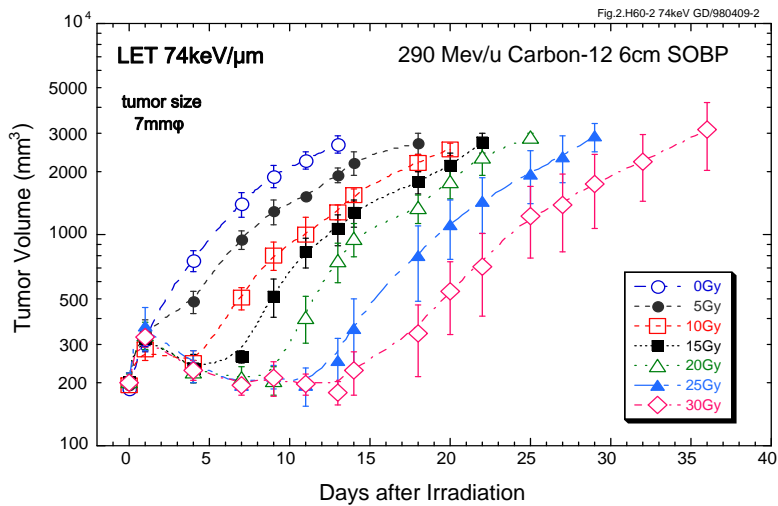
Fig.4



Reoxygenation

Tumor oxygen status changes after irradiation so that reoxygenation takes place during fractionated irradiation. Here tumor growth delay is measured after irradiation (Fig.5) (Ando, unpublished data) .

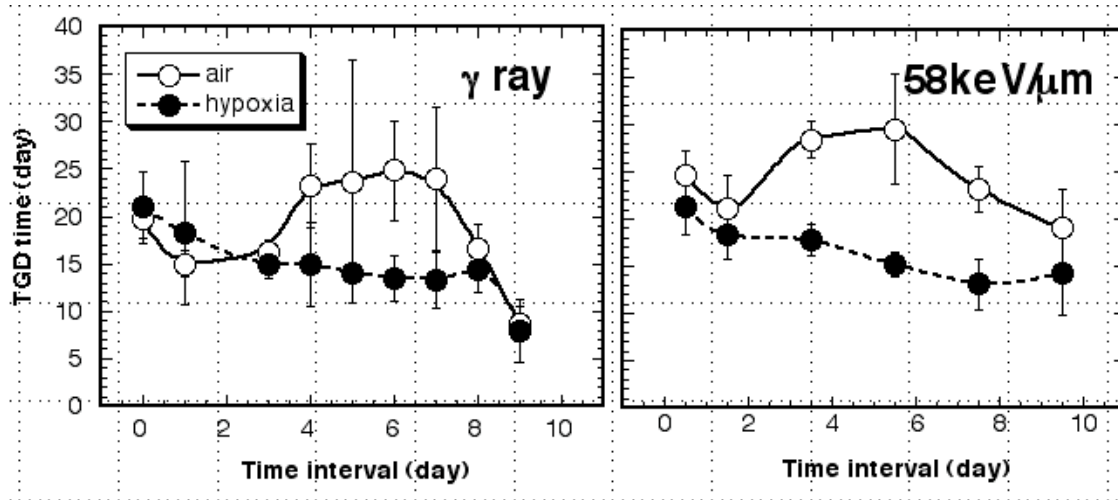
Fig.5



Tumor reoxygenation is measured by a method that involves an initial irradiation, which is followed by a second irradiation under conditions of either intact or clamped blood supply. When the tumor growth delay is longer for the intact than for the clamped blood supply, the tumor is reoxygenated.

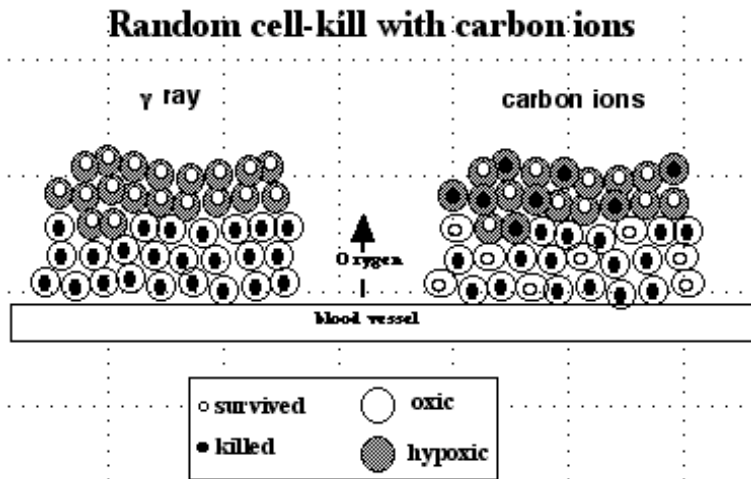
As seen in figure 6, tumor reoxygenation is accelerated after carbon ions compared to γ -rays (Ando 1999).

Fig.6



One explanation for the acceleration of tumor reoxygenation with carbon ions may be the random killing of both oxic and hypoxic cells with carbon ions allowing more reoxygenation (Fig.7).

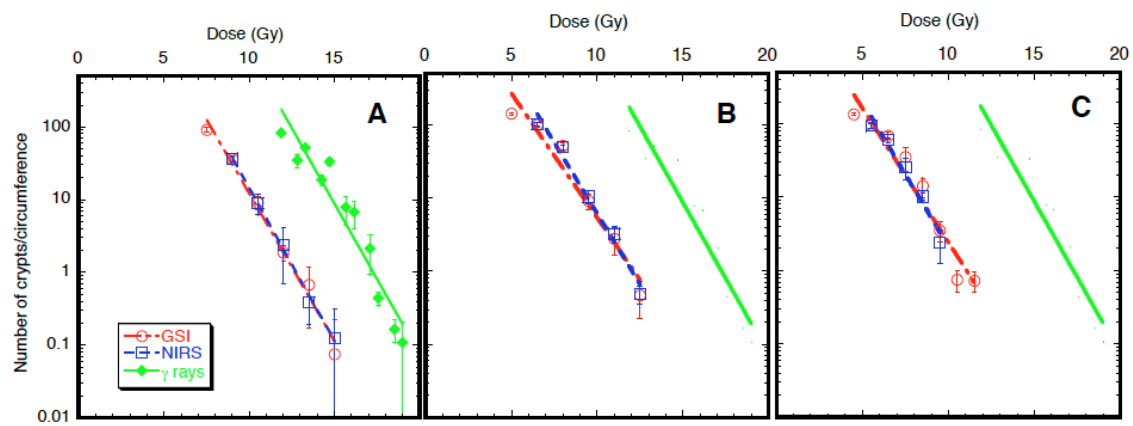
Fig.7



Normal tissue damage

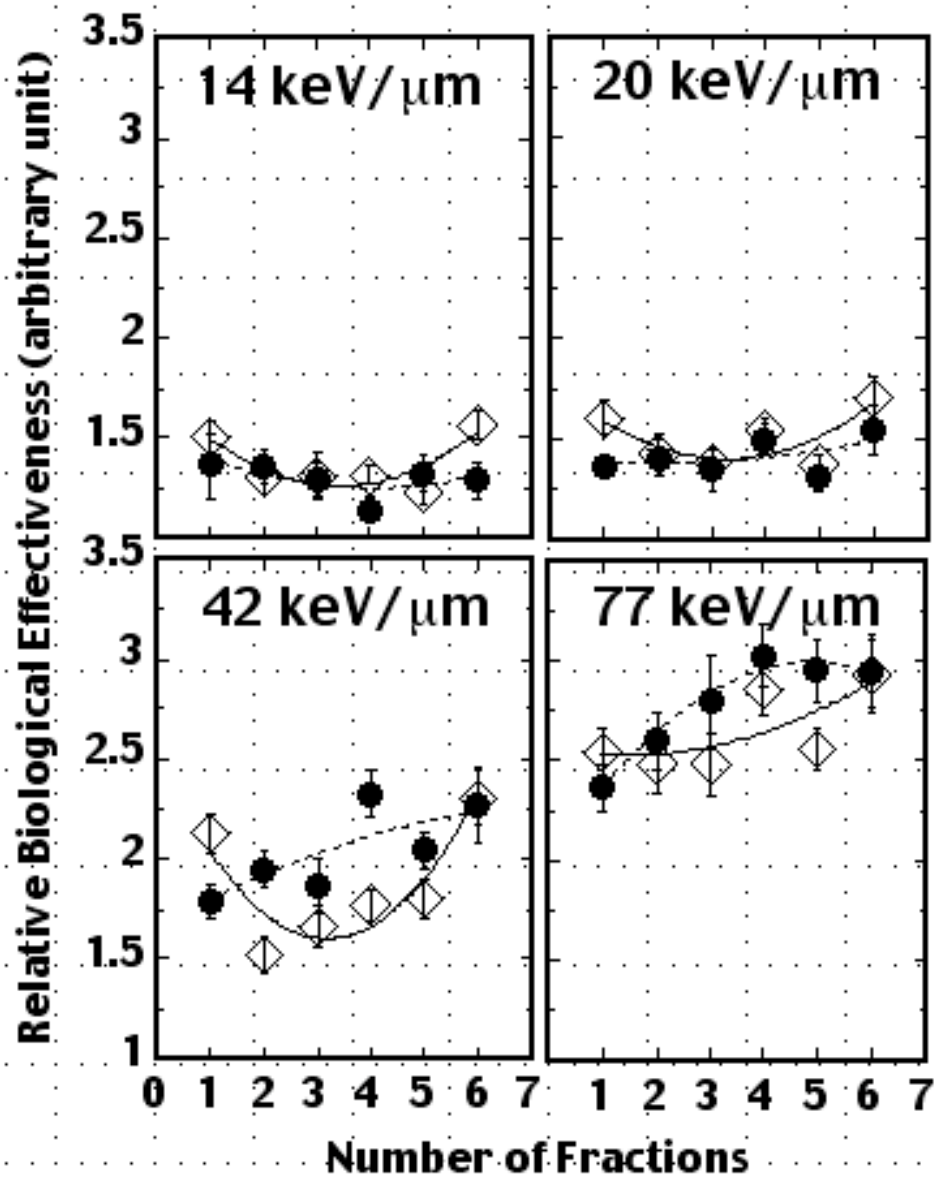
Mouse jejunum crypt survivals have been studied after irradiation with carbon ions at NIRS and GSI (Fig.8) (Uzawa 2009). Survival curves for the 2 institutions are similar at 3 different positions within a 6-CM SOBP (Spread-Out Bragg peak), indicating beam spreading methods at each facility do not change the biological effectiveness of carbon ions.

Fig.8



The therapeutic gain of carbon ions has been studied by comparing RBE (Relative Biological Effectiveness) between tumor and skin. Figure 9 shows

Fig.9

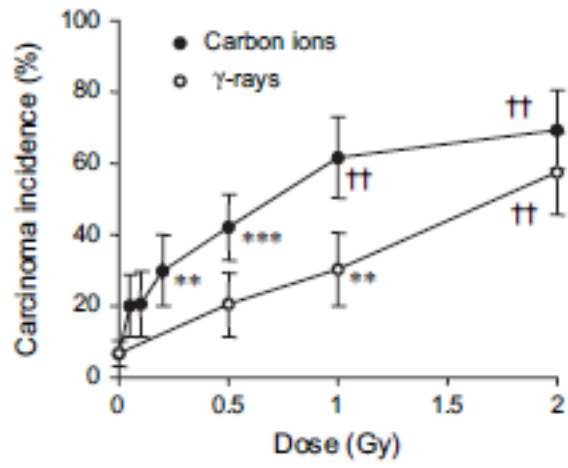


that the RBE for tumor control is greater than that for the skin response when both tissues are irradiated with 3-5 dose fractions of the SOBP but not the entrance plateau of 290 MeV/u carbon ions (Ando2005).

The risk of secondary tumors induced by carbon-ion beams has also been studied *in vitro* and *in vivo* (Imaoka 2007). Secondary mammary carcinomas are more prevalent in Sprague-Dawley rats

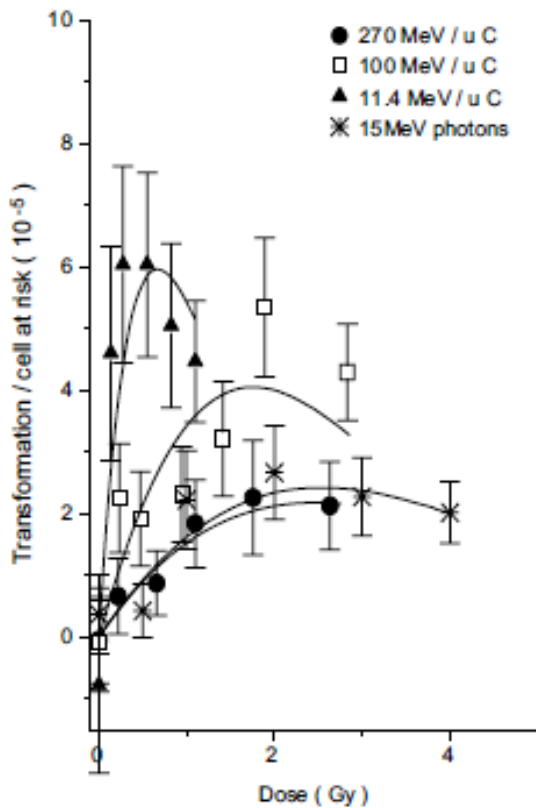
irradiated with 290 MeV/u carbon ions (LET 40–90 keV/μm) (Fig.10).

Fig.10



The transformation induction for high-energy (therefore low LET) carbon ions is comparable to that for photons, whereas for carbon ions of lower energies, the probability of transformation in a single cell is greater than that for photons (Fig.11) (Bettega 2009). The LET values for the accelerated carbon ions shown in figure 11 are 13.5 keV/μm (270 MeV/u), 26.4 keV/μm (100 MeV/u) and 149 keV/μm (11.4 MeV/u).

Fig.11



3. Clinical studies

At the NIRS, carbon-ion radiotherapy has been completed using 50 protocols on over 4000 patients with a variety of tumors. Carbon-ion radiotherapy is effective in such regions as the head and neck, skull base, lung, liver, prostate, bone and soft tissues, and pelvic recurrence of rectal cancer, as well as for histological types including adenocarcinoma, adenoid cystic carcinoma, malignant melanoma and various types of sarcomas. The number of irradiation sessions per patient and the overall treatment time has been reduced compared to conventional radiotherapy and averages 13 fractions spread over approximately three weeks. A new therapy facility is under

construction at NIRS where rotatable gantry and spot-scanning will be used for carbon-ion radiotherapy.

Treatment planning and dose prescription

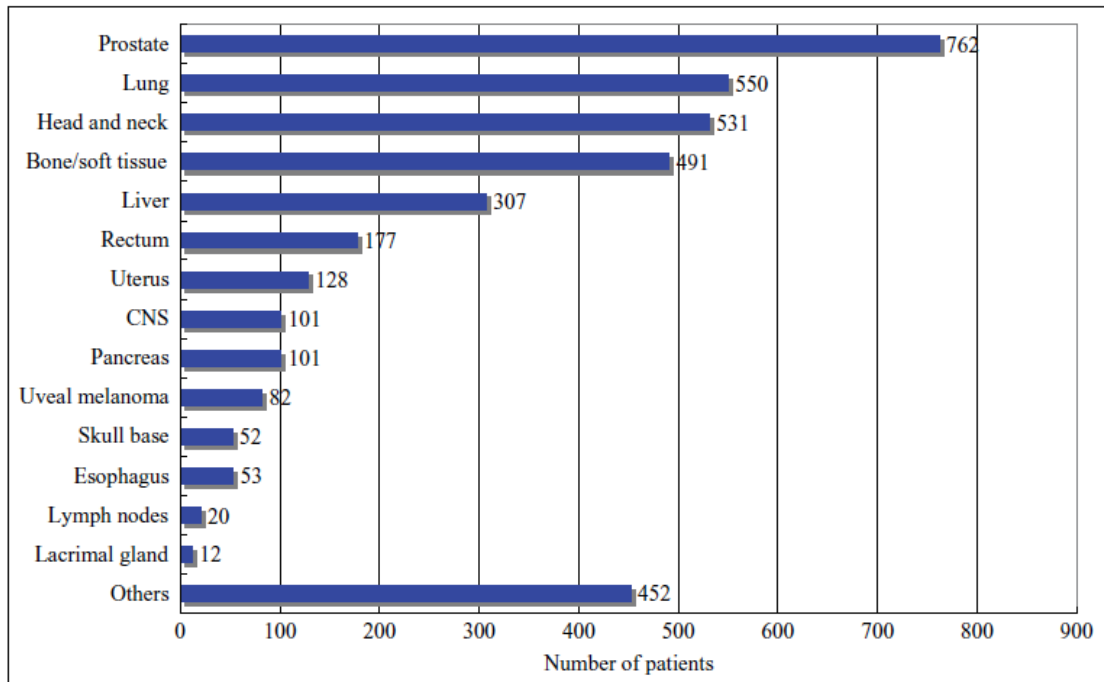
The first preparatory procedure for Carbon-ion radiotherapy is the fabrication of custom-made immobilization devices for each patient. Planning-CT scans are taken with the patients wearing these devices. The CT image data obtained in this manner are transferred to the treatment planning system, in which delineation of target volumes is made by physicians using CT images or fusion images consisting of CT, MRI and PET images. Patient-specific irradiation parameters are then determined for designing the bolus and collimators for selective irradiation of the tumor strictly in accordance with these parameters. Radiation delivery is performed by the passive method using modulators, collimators and compensators. If the patient requires respiratory-gated irradiation, respiration-synchronizing devices are also used for them at the time of the CT scans.

The dose is indicated in GyE, calculated by multiplying the physical carbon dose (Gy) by RBE so as to permit a comparison with photon beams: $\text{GyE} = \text{physical dose} \times \text{RBE}$. Irrespective of the length of the SOBP, the RBE of the carbon-ion beams used for radiotherapy is 3.0 at the distal part of the SOBP. This value is identical with the RBE previously used in fast neutron radiotherapy at NIRS.

Number of patients

The number of patients treated to date with carbon ions varies depending on tumor location. Prostate tumor is the most frequently treated condition, followed by lung, head and neck, and bone/soft tissue tumors (Fig.12) (Tsuji 2008).

Fig.12



Clinical outcome

The clinical outcome of carbon radiotherapy varies, depending on tumor sites and protocols. Table 1 and 2 show the summary of survival rates of patients (Tsuji 2007). In short, prostate tumors show more than 90% 5-year survivals. Uterus cervix tumors range from 40% to 60%, bone/soft tissue sarcomas 40% to 80 %, head and neck 30% to 70 %, tumors at skull base/cervical spine 90%, lung tumors 20% to 50% and liver tumor 30% to 70 %.

Table 1 Results of carbon Ion Radiotherapy at NIRS (Treatment Period : 6.1994~2.2006) (Part 1)

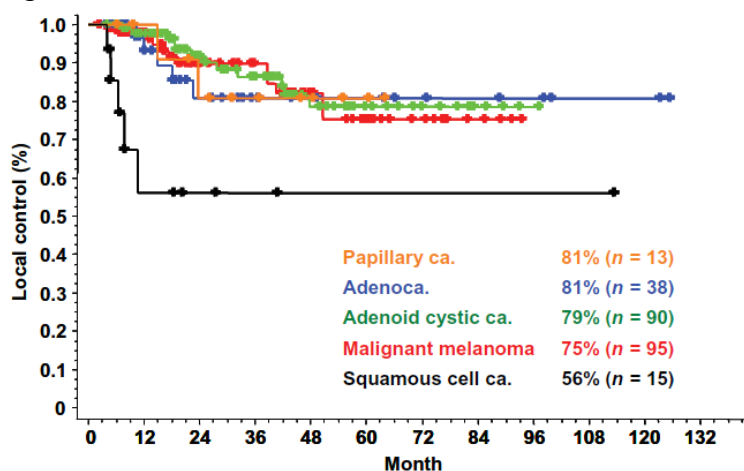
Protocol	phase	Tumors	C-ion RT GyE./frs./wk	No. Patient s	3-year Local Control	Overall Survival		Comments
						3-yr	5-yr	
Head & Neck-1+2	I/II	Locally advanced	49~70/16~18/4~6	34	81%	48%	37%	*4-yr survival
Head & Neck-3	II	Locally advanced	57.6/16/4	224	77%	57%	43%	
		-Adenoid cystic ca		64	82%	76%	68%	
		-Adenocarcinoma		26	72%	64%	64%	
		-Malignant melanoma		80	88%	49%	30%	
		-Others		54	55%	46%	27%	
Head & Neck-4	I/II	Sarcoma	70.4/16/4	16	100%	56%	56%*	
Head & Neck-5	II	Malignant melanoma	57.6/16/4	57	82%	42%	35%*	
		-C-ion + Chemotherapy		48	92%	45%	45%*	
Skull base/ cervical spine	I/II	Skull base/cervical spine	48.0~60.8/16/4	40	93%	94%	87%	
		-Chordoma		25	88%	100%	86%	
Lung-1	I/II	Stage I (Peripheral type)	59.4~95.4/18/6	47	65%	-	42%(61%)*	*Figures in () indicate cause specific survival
Lung-2	I/II	Stage I (Peripheral type)	72.0~79.2/9/3	34	91%	-	41%(90%)*	
Lung-3	II	Stage I (Peripheral type)	72.0/9/3	50	95%	-	50%(76)*	
Lung-4	I/II	Stage I (Peripheral type)	52.8~60.0/4/1	79	90%	-	41%(62)*	
Lung-3+4	-	Stage I (Peripheral type)	4 and 9 fractions	129	98%	-	57%(79)*	
		-I A(<3 cm)		71	99%	-	63%(90)*	
		-I B(>3 cm)		58	90%	-	50%(63)*	
Lung-5	I/II	Stage I (Peripheral type)	28~44 (Single day)	116		-	-	
Lung-6	I/II	Stage I Central type)	57.6~61.2/9/3	23	91%	-	21%(39)*	
Lung-7	I/II	Locally advanced	68~76/16/4	37	88%	-	38%(55)*	
Liver-1	I/II	T2~4 MONO	49.5~79.5/15/5	24	81%	50%	25%	*Bil<1.5, ICG<23%
Liver-2	I/II	T2~4 MONO	48~70/4~12/1~3	82	87%	48%	26%	
Liver-3	II	T2~4 MONO	52.8/4/1	44	95%	58%	35%	
Liver-2+3	-	All cases treated with 4 frs	52.8/4/1	51	94%	57%	33%	
		-with good liver function*	52.8/4/1	22		77%	54%	

Table 2 Results of carbon Ion Radiotherapy at NIRS (Treatment Period : 6.1994~2.2006) (Part 2)

Protocol	phase	Tumors	C-ion RT GyE / frs / wk	No. Patients	3-year Local control	Overall Survival		Comments
						3-yr	5-yr	
Prostate-1	I/II	B2-C	54~72/20/5	35	97%	94%	89%	5-yr bNED Survival ---91%
Prostate-2	I/II	A2-C	60-66/20/5	61	100%	97%	90%	---78%
Prostate-3	II	T1C-C	66/20/5	333	99%	94%	91%	---87%
Prostate- 2+3	Total	A2-C	66/20/5	374	99%	95%	92%	---88%
		-Low risk		68	98%	98%	93%	---87%
		-High risk		306	100%	94%	91%	---89%
		-PSA<20		216	99%	96%	91%	---89%
		-PSA>20		158	100%	94%	92%	---88%
Cervix-1	I/II	II-IVa (Sq,Cell Ca)	53~72/24/6	30	49%	40%	37%	
Cervix-2+3	I/II	II-IVa (Sq,Cell Ca)	64~72/20~24/5	36	69%	52%	42%	
		-Stage III			72%	55%	41%	
		-Stage Iva			63%	38%	38%	
Uterus (Adenoca)	I/II	II-Iva (Adenoca)	62.4~71.2/20/5	39	72%	68%	36%	
Bone-Soft tissue-1	I/II	Unresectable	53~74/16/4	57	63%	47%	36%	Eligibility criteria includes the tumor located in the pelvis and para-spinal region.
Bone-Soft tissue-1	II	Unresectable	70.4/16/4	190	82%	67%	54%	
Bone-Soft tissue-1+2	-	Osteosarcoma	70.4/16/4	48	69%	51%	34%	
		Chorodoma	70.4/16/4	69	98%	91%	80%	
Rectum-1		Pelvic recurrence	67.2~73.6/16/4	65	82%	65%	55%	
Pancreas								
Preope C-ion-1	I/II	Resectable All	44.8~48.0/16/4	22	-	23.8% (2-yr) *		* Resected pats: 36.3%
Preope C-ion-2	I/II	Resectable All	30.0~33.2/8/2	11	-	18.0%(2- yr)**		**Resected pats: 40.0%
Radical C-ion	I/II	Unresectable All	38.4~48.0/12/3	31	-	38.0%(1- yr)		

Figure 13 shows local control rates for head and neck patients after carbon-ion radiotherapy (Tsujii 2008). Many tumors respond well to carbon-ion radiotherapy, while squamous cell carcinomas show only moderate responses.

Fig.13



Summary

Described here is a brief review of carbon ion radiotherapy for physicians and scientists with some background in the field of radiation therapy. Readers could find a detailed review article on biological effects of high LET radiation (Ando and Kase (2009))

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