Clinical advantages of carbon-ion radiotherapy

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Abstract. Carbon-ion radiotherapy (C-ion RT) possesses physical and biological advantages. It was started at NIRS in 1994 using the Heavy Ion Medical Accelerator in Chiba (HIMAC); since then more than 50 protocol studies have been conducted on almost 4000 patients with a variety of tumors. Clinical experiences have demonstrated that C-ion RT 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, against which photon therapy could be less effective. Furthermore, when compared with photon and proton RT, a significant reduction of overall treatment time and fractions has been accomplished without enhancing toxicities. Currently, the number of irradiation sessions per patient averages 13 fractions spread over approximately three weeks. This means that in a carbon therapy facility a larger number of patients than is possible with other modalities can be treated over the same period of time.

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1. Introduction

Carbon-ion beams are unique in that they not only exhibit a superior physical dose distribution, but also their biological efficiency increases with depth, reaching a maximum at the end of the beam’s range. This is based on the fact that, as ion beams travel deeper inside the body, the rate at which ion beams lose energy increases with depth. Consequently, this advantage of carbon ions is most pronounced for tumors demonstrating a low radiosensitivity to photon beams.

At the National Institute of Radiological Sciences (NIRS), clinical research on charged particle RT was started in 1994 using carbon-ion beams generated by the Heavy Ion Medical Accelerator in Chiba (HIMAC). Subsequently, two other facilities started this therapy at the Gesellschaft für Schwerionenforschung (GSI) in Germany in 1997 and the Hyogo Ion Beam Medical Center in Japan in 2004. In these facilities the clinical efficacy of carbon-ion radiotherapy (C-ion RT) has been prospectively investigated in a variety of tumors. Almost 4000 patients have been treated at NIRS, where the benefit of C-ion RT over other modalities has been demonstrated in terms of anti-tumor effects and a significant reduction in overall treatment time has been accomplished with acceptable toxicities [1]. More than 300 patients have undergone therapy at GSI, where promising results have been reported in skull base tumors and head and neck tumors. At the third carbon therapy facility at Hyogo, about 300 patients have been treated with similar results. Currently, still more are under construction or in planning, including three in Germany and one each in Italy, France and Japan.

This paper presents an overview of the 13-year experience with C-ion RT conducted at NIRS.

2. Methods and materials

2.1. Physical and radiobiological properties of carbon ions

Conventional photon and neutron beams are characterized by an exponential decrease in their dose profile with depth, while carbon ions share with protons the property of forming a high-dose region, known as the Bragg peak, at a finite depth. The peak is typically narrow, beyond which only a small dose due to secondary fragments is deposited. The original peak is too narrow and sharp to be used directly for the treatment of lesions of different shapes and sizes.
Modification of the narrow peak is therefore performed to conform to the size and shape of the lesion, creating a spread-out Bragg peak (SOBP).

In order to estimate the biological effect in charged particle therapy, the density of ionization events in the medium or linear energy transfer (LET) is used. It is generally known that the radiobiological effect or relative biological effectiveness (RBE) increases with an increase in LET. Carbon-ion and neutron beams, when compared to proton and photon beams, exhibit a larger energy loss and are described as high-LET radiation. While the LET of neutron beams remains uniformly high at any depth, the LET of carbon-ion beams increases steadily from the point of entrance in the body with increasing depth, reaching a maximum in the peak region. This results in the advantage of carbon-ion therapy, that not only the physical dose but also the biological effect is higher in the SOBP.

Because of its unique physical and biological properties, it is theoretically possible in C-ion RT to perform a hypofractionated RT using a significantly smaller number of fractions than has been used in conventional photon RT. This has been suggested by experiments with neutron beams and carbon-ion beams, providing the biological rationale for the validity of a short-course, hypofractionated regimen with high-LET radiation. Experiments conducted with fast neutrons and carbon ions have demonstrated that increasing the dose per fraction tended to lower the RBE of both the tumor and normal tissues. The RBE of the tumor, however, did not decrease as rapidly as the RBE of normal tissues [2, 3]. These experiments corroborate the assumption that the therapeutic ratio could increase when hypofractionated schemes are used in C-ion RT.

### 2.2. Materials

In June 1994, C-ion RT was initiated at NIRS, and the total number of patients enrolled until February 2008 was 3819 patients (4053 lesions) with a variety of tumors (figure 1). Most of the patients were treated in prospective phase-I/II and phase-II studies to confirm the safety and efficacy of C-ion RT and to obtain deeper understanding of this modality. The number of patients enrolled has been increasing year after year, primarily based on the fact that the treatment techniques became established and smoothly executed, and also because the number of fractions and the treatment period per patient were able to be significantly reduced over time. The overall treatment time for therapy in a year was around 40–43 weeks, which by maintenance work was divided into the first term (17.0–18.5 weeks) and the second term (23.0–24.5 weeks).

In the current analysis, we selected the population with major types of tumors involving the skull base, head and neck, lung, liver, prostate, rectum, and bone and soft tissues.

### 2.3. Treatment planning and dose prescription

The first preparatory procedure for C-ion RT is the fabrication of custom-made immobilization devices for each patient. The 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 [4, 5]. If the patient requires respiratory-gated
irradiation, respiration-synchronizing devices are also used on them at the time of the CT scans [6].

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: GyE = 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 of fast neutron beams, which were previously used in fast neutron radiotherapy at NIRS [4].

For finding an appropriate dose level in dose-escalation studies, the radiation dose was escalated by increasing the fraction size, while keeping both the fraction number and the length of treatment constant. The treatment was provided 4 days a week and the radiation dose was increased in increments of 5–10% up to the dose level at which tolerance might be reached. In recent years, the average number of treatment fractions per patient has been around 13 and the average treatment period about 3 weeks. For stage-I lung and liver cancers, treatment is carried out in single fractions and double fractions, respectively. For head and neck cancers, prostate cancer and bone/soft tissue tumors, treatment is completed in 16 fractions over 4 weeks, which is about half the number of fractions or even less than that in x-ray RT or proton-beam RT.

3. Results

3.1. Toxicities

About half of the patients were treated in phase-I/II dose-escalation studies aimed at determination of optimal dose fractionations for a variety of tumors. When escalating the
Table 1. Optimal dose-fractionations determined in dose escalation studies for carbon ion radiotherapy at NIRS.

| Tumor sites                  | Dose-fractionation (GyE/fr/week) | Gy/fr | BED (α/β = 10) | (α/β = 2.5) |
|------------------------------|----------------------------------|-------|----------------|-------------|
| Skull base                   | 60.8/16/4                        | 3.8   | 83.9           | 153.2       |
| H & N: ACC, MM etc           | 57.6/16/4                        | 3.6   | 78.3           | 140.5       |
| Sarcoma                      | 64.0/16/4                        | 4.0   | 89.6           | 166.4       |
| NSCLC: Peripheral type (Stage I) | 70.4/16/4                     | 4.4   | 101.4          | 194.3       |
| Hidr type                    | 90.0/18/5                        | 5.0   | 135.0          | 270.0       |
| Liver: HCC                   | 72.0/9/3                         | 8.0   | 129.6          | 302.4       |
| HCC                          | 52.8/4/1(T1)                     | 13.2  | 122.5          | 331.6       |
| 60.0/4/1(T2)                 | 15.0                            |       | 150.0          | 420.0       |
| 40.0 or 44.0/1/1day          | 40.0 or 44.0                     |       | --             | --          |
| Prostate                     | 68.4/12/3                        | 5.7   | 107.4          | 224.4       |
| Bone/soft tissue (pelvis)    | 79.5/15/5                        | 5.3   | 121.6          | 248.0       |
| 63.0/20/5                    | 5.8                            |       | 110.0          | 231.1       |
| Bone/soft tissue (paraspinal)| 58.0/8/2                        | 7.2   | 100.1          | 226.2       |
| Bone/soft tissue (paraspinal)| 52.8/4/2                        | 13.2  | 122.5          | 331.6       |
| Bone/soft tissue (paraspinal)| 38.8/2/2 days                   | 19.4  | 114.1          | 339.9       |
| Bone/soft tissue (paraspinal)| 19.4                            |       | 114.1          | 339.9       |
| Bone/soft tissue (paraspinal)| 66.0/20/5                       | 3.3   | 87.8           | 153.1       |
| Bone/soft tissue (paraspinal)| 63.0/20/5                       | 3.2   | 82.8           | 142.4       |
| Bone/soft tissue (paraspinal)| 57.6/16/4                       | 3.6   | 78.3           | 140.5       |
| Rectum (post-op recurrence)  | 70.4/16/4 (pelvis)               | 4.4   | 101.4          | 194.3       |
| Bone/soft tissue (paraspinal)| 64.0/16/4 (paraspinal)          | 4.0   | 89.6           | 166.4       |
| Bone/soft tissue (paraspinal)| 73.6/16/4                       | 4.6   | 107.5          | 209.0       |
| Bone/soft tissue (paraspinal)| 74.4/20/5                       | 3.7   | 102.1          | 185.1       |

Total dose, better local control is expected with larger doses, but adverse reactions become more serious. It is desirable to terminate the dose-escalation studies immediately before severe adverse reactions develop. In the early phase of the studies, however, the patients with prostate cancer and uterine cervix cancer, who were irradiated with the highest doses, developed severe gastrointestinal side effects [7, 8]. After the cause of these side effects was examined in detail, the safe dose was determined and irradiation techniques were improved when no more similar side effects were observed.

3.2. Local control and survival

Table 1 summarizes the dose-fractionations that were determined as optimal in dose-escalation studies for various types of tumors.
3.2.1. Skull base tumors. There were 46 patients with skull base tumors, including chordoma (29), chondrosarcoma (7), meningioma (6), olfactory neuroblastoma (3) and giant cell carcinoma (1). The total dose was escalated from 48.0 to 60.8 GyE given in 16 fractions over 4 weeks. Local control was achieved in 74% for chordoma, 100% for chondrosarcoma and 80% for meningioma. At the higher total doses, improvement of tumor control was observed and no severe adverse reactions developed. For chordoma, the fractionation regimen of 60.8 GyE/16 fractions/4 weeks yielded the best local control of 91% at 5 years, whereas local control was only 60% after 48.0–57.6 GyE. The overall 5-year survival rates were 88% in 17 patients with chordoma, 54% in chondrosarcoma and 83% in meningioma. There were 3 deaths with chondrosarcoma, all of them dying of intercurrent disease.

3.2.2. Head and neck tumors. Seventeen patients were treated in the first phase-I/II study using a fractionation regimen of 18 fractions over 6 weeks, the same regimen as previously used in fast neutron therapy in NIRS. Thereafter, 19 patients were treated in the second phase-I/II study using a fractionation regimen of 16 fractions in 4 weeks. Most patients had locally advanced tumors in the nasal cavity and accessory nasal sinus with infiltration into the skull base. The results of these two studies were reported previously [9]. In brief, no difference between the two was found in terms of morbidity and local control, and specific effectiveness was shown in the local control of non-squamous cell histology such as adenoid cystic carcinoma and malignant melanoma. There was no clear relationship between the total dose and visual acuity, but the target volume irradiated was an important factor [10]. Based on these results, it was decided to adopt the shorter fractionation regimen of 16 fractions over 4 weeks in the subsequent studies.

Between April 1997 and August 2007, a total of 295 patients were treated in the third study using 57.6 or 64.0 GyE given in 16 fractions over 4 weeks. The major histological types included malignant melanoma (95), adenoid cystic carcinoma (90) and adenocarcinoma (37), and the major tumor sites included paranasal sinus (75), nasal cavity (63), salivary gland (37), and oral cavity (34). Local control was achieved in 75–81% of the patients with adenocarcinoma, adenoid cystic carcinoma and malignant melanoma. However, it was only 56% for squamous cell carcinoma because more advanced tumors were included in this histological type (figure 2). Mucosal malignant melanoma was the most common histological type, and a total of 95 patients with this tumor were treated. Local control was 75%, but survival was only 36% due to distant metastasis. Based on this result, a new protocol was designed for treatment of malignant melanoma, using C-ion RT and concomitant chemotherapy. To date, a total of 64 patients have been treated, and the 5-year local control and survival rates are 78.8 and 48%, respectively. It is assumed that the better tumor control has prevented distant metastasis and resulted in prolonged survival in malignant melanoma.

Twenty-five patients with bone and soft tissue sarcomas in the head and neck regions were treated with a total dose of 70.4 GyE given in 16 fractions. The histological types included osteosarcoma (9), malignant fibrous histiocytoma (5) and other histologies (11). The 5-year local control and 5-year survival rates were 100 and 35.8%, respectively.

3.2.3. Non-small-cell lung cancer (NSCLC). It is assumed that, in radiotherapy of stage-I (T1-2N0M0) NSCLC, tolerance of normal lung tissues could be different depending upon the location of the tumor. Therefore, this tumor was divided into the peripheral- and central-types,
with each type being treated with a different fractionation regimen. For this tumor, we have been conducting clinical studies for establishing a short-course, hypofractionated radiotherapy.

For peripheral-type NSCLC, we started a dose-escalation study using 18 fractions/6 weeks, which was the same as was used for head and neck tumors. The number of fractions and treatment times were subsequently carefully reduced to 9 fractions over 3 weeks, 4 fractions over one week, and eventually to a single fraction a day (figure 3). The respiratory-gated irradiation method, a technique synchronizing with the respiratory movement of target organs, was used [6]. Irradiation from 3- to 4-field directions was found to be less toxic than that via 1–2-field directions. Adverse reactions in the lung increased as the dose increased, and there was a clear relationship between the total dose and local tumor control. The results of treatment using 18, 9 and 4 fractions were reported previously [11]–[13].

In the current analysis, a total of 129 patients treated with 9 fractions/3 weeks (50 patients) and 4 fractions/1 week (79 patients) were evaluated. All the patients were treated more than 5 years ago and none of them developed severe toxicities. After C-ion RT, the 5-year local control rates were 98.6% for stage-IA cases and 89.7% for stage-IB cases, and the 5-year survival rates were 63.1% for stage-IA cases and 50.0% for stage-IB cases (figure 4).

Single-fraction irradiation is the ultimate regimen utilizing the advantage of carbon-ion beams. Since 2003, a phase-I/II dose-escalation study using single fraction C-ion RT has been underway for peripheral-type lung cancer. The total dose has been escalated from 28.0 to 44.0 GyE at increments of 5%. So far, no serious adverse events have been observed, and local control appears to be improving with increases in total dose.

C-ion RT has also been applied to locally advanced lung cancers and hilar-type cancers, and case studies are being accumulated. The locally advanced lung cancers included Pancoast tumors and mediastinal-type tumors in stages II–IIIA. The overall local control rate was 92.7%, and the cause-specific survival rate at 46 months was 52.7%.
3.2.4. **Hepatocellular carcinoma (HCC).** For HCC, dose-escalation studies have been carried out on 5 different fractionations for establishing a short-course irradiation method (table 2). The result of the first phase-I/II study on 24 patients using 49.5–79.5 GyE in 15 fractions/5 weeks was reported previously [14]. In brief, the local control and overall survival rates at 3 and 5 years were 81 and 50%, and 81 and 25%, respectively. Thereafter, shorter fractionated regimens of 12 fractions/3 weeks, 8 fractions/2 weeks, 4 fractions/1 week and 2 fractions/2 days have been successively investigated. Regarding the morbidity after C-ion RT, 4 patients (3%) developed liver dysfunction of grade 3 or higher, which eventually returned to the pre-treatment level with conservative treatment. The largest number of 75 patients was treated with a total dose ranging from 48.0 to 52.8 GyE in 4 fractions. Of them, 61 patients were treated with 52.8 GyE, and their 3-year local control and 5-year survival rates were 94 and 34%, respectively. In 20 patients with a tumor diameter of 3–5 cm, the 3- and 5-year survival rates were 75 and 70%, respectively.

### Table 2. Local control and morbidity of carbon ion RT in hepatocellular carcinoma.

| Fractionation | Local control | Morbidity (3–12 mo) |
|---------------|---------------|---------------------|
|               | 3-yr LC No.   | 0 1 2 3 4           |
| TD/Fx/Wk      |               |                    |
| 49.5–79.5/15 fx/5 wk | 24 81% | 20 10 4 5 1(15%) 0 |
| 54.0–69.6/12 fx/3 wk | 34 86% | 24 16 2 6 0(0%) 0 |
| 48.0–58.0/8 fx/2 wk | 24 86% | 16 10 5 0 1(6%) 0 |
| 48.0–52.8/4 fx/1 wk | 75 90% | 54 40 6 6 2(4%) 0 |
| 32.0–38.8/2 fx/2 day | 36 90% | 13 9 2 2 0(0%) 0 |
| **Total**     | 181 –        | 127 85 19 19 4(3%)* 0 |

*All recovered to pre-treatment function.
Figure 4. Local control and survival in stage-I non-small cell lung cancer treated with 4 and 9 fractions.

Since April 2003, a dose-escalation study has been performed in 36 HCC patients, delivering a total dose of 32–38.8 GyE in 2 fractions over 2 days [15]. No patients developed severe side effects, and the 3-year local control and survival rates were 84 and 77%, respectively. It was decided for the 2-fraction RT to adopt a total dose of 38.8 GyE or larger. Regarding side effects after C-ion RT, there were few limitations due to liver dysfunction or tumor diameter, and more than 90% of the patients were free of symptoms during and after the treatment. Patients with tumors not contacting the gastrointestinal tract, moderate or higher liver function, and a tumor diameter of 10 cm or less are considered to be good candidates for C-ion RT.

3.2.5. Prostate cancer. The total number of patients treated was 760 by February 2008. After the early dose-escalation study was terminated [7], patients were successively treated with three different fractionation regimens using 66 GyE/20 fractions/5 weeks, 63 GyE/20 fractions and 57.6 GyE/16 fractions. The radiation regimen of 66 GyE/20 fractions/5 weeks had been used until January 2005, when the total dose was reduced to 63 GyE to further decrease the incidence of adverse reactions. In an effort to reduce the treatment period from 5 to 4 weeks, we decided to use 57.6 GyE given in 16 fractions, which is currently the standard fractionation regimen for all prostate cancers.

Patients were classified into two groups—high- and low-risk groups—based on factors including PSA, Gleason score and TNM classification for determining the need of combination with endocrine treatment. The high-risk group was treated with C-ion RT in combination with endocrine therapy for 2 years or longer, and the low-risk group was treated with C-ion RT alone. The results of these treatments were reported previously [16, 17]. Since September 2005, those patients considered not to require long-term hormone therapy were separated from the high-risk group as a medium-risk group, for whom the period of the hormone therapy was reduced to 6 months.

The incidence of morbidity scored at the maximum reactions and at the time of the last follow-up in the rectum and lower urinary tract (bladder/urethra) is listed for three different regimens in table 3. No patients developed reactions of grade 3 or higher after the optimal irradiation dose was established. The incidence of adverse reactions of grade 2 with the current technique ranged from 1.1 to 2.7% in the rectum and from 0 to 7.8 % in the lower urinary tract,
Table 3. The incidence of morbidities scored at the maximum reactions and at the time of the last follow-up after carbon ion therapy in patients with prostate cancer. The median follow-up period is 52.1 months for 66.0/20f, 8.9 months for 63.0/20f and 26.2 months for 57.6/16f.

| Dose GyE/f | No. pts | Rectum G0 | G1 | G2 | G3 | Bladder/urethra G0 | G1 | G2 | G3 |
|------------|---------|-----------|----|----|----|-------------------|----|----|----|
| Maximum    |         |           |    |    |    |                   |    |    |    |
| 66.0/20f   | 255     | 80.0      | 17.3 | 2.7 | 0   | 31.0              | 61.2 | 7.8 | 0   |
| 63.0/20f   | 162     | 89.5      | 9.3  | 1.2 | 0   | 64.2              | 34.0 | 1.9 | 0   |
| 57.6/16f   | 87      | 88.5      | 10.3 | 1.1 | 0   | 71.3              | 28.7 | 0   | 0   |
| Last F/U   |         |           |    |    |    |                   |    |    |    |
| 66.0/20f   | 255     | 92.9      | 5.9  | 1.2 | 0   | 77.6              | 18.8 | 3.5 | 0   |
| 63.0/20f   | 162     | 95.1      | 4.3  | 0.6 | 0   | 80.9              | 17.9 | 1.2 | 0   |
| 57.6/16f   | 87      | 95.4      | 3.4  | 1.1 | 0   | 90.8              | 9.2  | 0   | 0   |

and they have tended to decrease as the time after irradiation elapsed. The current treatment with 57.6 GyE/16 fractions has produced no reactions of grade 2 or higher in 87 patients observed for 6 months or more, and this regimen is considered to be comparable to or even safer than the treatment with 63 or 66 GyE given in 20 fractions.

For the 466 patients treated with 63 or 66 GyE/20 fractions/5weeks and observed for 6 months or longer, the 5-year local control rate was 99.2%, the 5-year survival rate was 94.8%, the cause-specific survival rate was 98.6% and the biochemical non-recurrence rate was 89.9%. 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.

Following a treatment with 57.6 GyE/16 fractions in 122 patients, only one patient had biochemical recurrence and none has died. This treatment is expected to produce results comparable to or better than 20-fractionated irradiation in terms of the anti-tumor effect with less risk of adverse reactions, giving great hope for future long-term results.

3.2.6. Bone and soft tissue tumors. C-ion RT was started in 1996 as a phase-I/II dose-escalation study for bone and soft tissue tumors not suited for resection. The majority of the patients had tumors arising from the pelvis, spine, paraspinal and retroperitoneal regions. Total dose was started at 52.8 GyE in 16 fractions over 4 weeks and increased to 73.6 GyE. The local control rate improved as the dose increased, but some patients given the largest dose developed severe skin and soft-tissue reactions. The results of the treatment in 57 patients were reported previously [18]. In the up-date analysis for the same patients, the 3-year local control rate was 63% and 3- and 5-year survival rates were 47 and 36%, respectively.

In the current analysis based on 323 lesions in 307 patients treated between April 2000 and August 2007, the 5-year local control and survival rates were 80 and 56%, respectively. Skin and soft-tissue toxicities developed as severe side effects in about 3% in the previous study, which has since been reduced to zero because of an effort to decrease the skin doses. In 58 patients with osteosarcomas in the pelvis or spine, the 5-year local control and survival rates were 65 and 29%, respectively. The result of the treatment for chordomas of the sacral bone was reported.
previously [19, 20] and appeared in The Year Book of Oncology in 2006 [21]. In the up-date analysis based on 103 patients with sacral chordoma, the 5-year local control and survival rates were 89% and 83%, respectively. A typical case of chordoma is shown in figure 5.

3.2.7. Postoperative pelvic recurrence of rectal cancer. Between April 2001 and August 2007, 95 lesions in 90 patients with locally recurrent rectal cancers without distant metastases were treated with C-ion RT. Total doses of 67.2, 70.4 and 73.6 GyE were delivered in 16 fractions over 4 weeks [22]. With respect to the side effects after C-ion RT, none of the patients developed severe reactions of grade 3 or worse (NCI-CTC) in both acute and late phases in the gastrointestinal tract, urinary tract and subcutaneous tissues. The treatment results were favorable; the local control rate was 88.6% at 3 years and 80.5% at 5 years and the overall survival rate was 60.0% at 3 years and 42.8% at 5 years. With increases in total dose, improvements of both local control and survival rates were observed (figure 6). There were 63 lesions in 61 patients treated with 73.6 GyE/16 fractions/4 weeks, and their 5-year local control and survival rates were 92.7 and 57.4%, respectively.

In terms of symptomatic response within 3 months after treatment, pain had reduced in 97% of the cases. Pain relief was maintained for one year in 67, 91 and 100% after irradiation with 67.2, 70.4 and 73.6 GyE, respectively.

3.2.8. Uterine cancer. Three clinical studies on C-ion RT have been conducted for advanced cervical squamous cell carcinoma of stages III B–IV A. Early in the clinical studies of 44 patients, several patients required surgical treatment because of severe complications in the intestinal tract [23]. In the later part of the studies, however, improvement in irradiation techniques was achieved, yielding better results in terms of safety and local tumor control.

A total of 46 patients with uterine adenocarcinoma, unsuited for surgical resection, were treated with C-ion RT. The total dose was escalated from 62.4 to 74.4 GyE given in 20 fractions over 5 weeks, with better local control at higher doses. The 5-year local control and survival
rates in 38 patients with uterine cervical adenocarcinoma were 64 and 42%, respectively, and the corresponding rates in 8 patients with corpus adenocarcinoma were 71 and 64%, respectively.

4. Discussion

In the world, ion-beam RT has a history of nearly 50 years with proton beams and nearly 30 years with heavier ions (24). C-ion RT has been performed since 1994 at NIRS and has shown favorable results in tumors resistant to low-LET radiations. It has been effective in regions such as the head and neck (including eyes), 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, HCC, and various types of sarcomas such as malignant melanoma and bone and soft tissue sarcomas, against which photon beams are less effective. In the early stages of the clinical trials for tumors in the lower abdomen, some patients developed intestinal ulcers or perforations at high doses, requiring surgery [7, 8], but similar types of severe complications were no longer observed after improvement in irradiation techniques.

In the current C-ion RT, fraction numbers per patient have been successfully shortened to an average of 13 fractions spread over about 3 weeks. The rationale for the short-course, hypofractionated RT lies on both the superior dose localization and the unique biological properties of carbon ions. This means that the facility can be operated more efficiently, offering treatment for a larger number of patients than is possible with other modalities over the same period of time. Hypofractionated RT has been applied against almost all types of tumors. In lung and liver cancers, for example, ultra-short-course irradiation to be completed in a single fraction or two fractions has been made possible. Even for head and neck cancers, prostate cancer, and bone and soft-tissue tumors requiring a relatively long course of RT, only 16–20 sessions have been sufficient, roughly half the number of fractions required when using standard RT.

In the treatment of skull base tumors, complete resections are rarely achieved and adjuvant high-dose RT is recommended after incomplete resection. Although there have been no randomized trials comparing photons and protons, a retrospective analysis has demonstrated that chordoma patients treated with protons had a better local control probability than with photons [24]. Similar results have been obtained with C-ion RT in the present study as well as at GSI [25]. In the case of chordoma, however, the available data show that, although a
significant improvement of 5-year local control is achieved with protons, the long-term 10-year outcome local control in the case of chordoma is not satisfactory [26]. In this regard, C-ion RT may have a possibility of further improving the long-term result.

In C-ion RT of head and neck tumors, favorable results have been obtained in non-squamous cell types of tumors such as adenocarcinomas, adenoid cystic carcinomas and malignant melanomas. At GSI, in the treatment of locally advanced adenoid cystic carcinomas, locoregional control rates for the combined photon IMRT and carbon ions were better than those observed in a historical series of patients treated with photon IMRT alone [27]. The current study has shown that the prevention of distant metastasis is an important issue for further improvement in survival of malignant melanoma. For this tumor, combination treatment with C-ion RT and chemotherapy has been in use at NIRS, and a significant improvement in the survival rate has been achieved.

In C-ion RT of stage-I peripheral-type NSCLC, no patients developed severe toxicities, and a local control rate of >90% was obtained. It is reported that the 5-year survival rate was 71.5% for stage-IA and 50.1% for stage-IB cancers in 7408 surgery cases included in a 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. When the survival rates were compared, the 3-year survival rate was 81.3% for stage-IA after surgery and 75.6% for C-ion RT, with no marked differences between the two in survival. Considering that the average age of the patients receiving C-ion RT was about 75 years, about 10 years older than that of 65 years in the operated patients, the results of C-ion RT for stage-I lung cancer may be almost comparable to the surgical results. Furthermore, short-course irradiation with 9 and 4 fractions was confirmed as a safe treatment for the peripheral-type stage-I lung cancer, for which surgery was not indicated or refused. A clinical study on a single fraction treatment is currently being conducted, and the preliminary results appear favorable.

The current analysis has demonstrated that C-ion RT for HCC appeared safe and effective even for patients with recurrent or locally advanced tumors with liver cirrhosis. It has promising potential as a new, radical and minimally invasive therapeutic option for HCC. In particular, favorable results have been obtained for those tumors with a diameter of 3–5 cm, comparable to or even better than the 3- and 5-year survival rates of 73 and 56% in patients with a tumor diameter of 2–5 cm receiving liver resection [28]. This suggests that locally confined lesions over 3 cm, up to 5 cm, are most suitable for C-ion RT.

For prostate cancer, a comparison of the biochemical non-recurrence rate in patients with a PSA level of 20 ng ml\(^{-1}\) or higher before treatment with those receiving other radiotherapies showed a markedly higher non-recurrence rate in those receiving C-ion RT. The high non-recurrence rate is likely also associated with the effects of our appropriate use of combination hormone therapy, but a comparison with clinical studies in Europe and North America that combined hormone therapy and x-ray RT showed that our survival rate was 10–15% higher [29], confirming that the high local effect of carbon-beam RT led to good treatment results (table 4). It is emphasized that, with hypofractionated regimen using 20 fractions over 5 weeks, no serious toxic reactions have been observed and the survival rate has been superior to other modalities, in particular for high-risk groups. Currently, even a shorter fractionation with 16 fractions over 4 weeks is being evaluated.

Bone and soft-tissue tumors are diseases for which multidisciplinary treatment, with the primary choice being surgical resection, has achieved favorable results over the past 20 years. When surgical resection is not indicated or is difficult to perform, radiotherapy is
Table 4. Comparison in survivals rates with results of RTOG meta analysis.

| Treatment                  | Dose (Gy/f) | OS\(^a\) in each risk group \(^b\) |
|----------------------------|-------------|------------------------------------|
|                            | Group 2     | Group 3                            | Group 4     |
|                            | No. pts     | 5-y OS    | No. pts     | 5-y OS    | No. pts     | 5-y OS    |
| RTOG meta analysis\(^c\)   |             |          |             |          |             |          |
| RT alone (65–70/35)        | 443         | 82%      | 338         | 68%      | 324         | 52%      |
| RT+ hormone                | 114         | 76%      | 138         | 79%      | 103         | 63%      |
| Carbon                     | 137         | 99%      | 154         | 94%      | 62          | 87%      |
| RT+ hormone (66.0/20)      |             |          |             |          |             |          |

\(^a\)Overall survival rate.

\(^b\)Risk group: Group 2, GS2-6, T3 or GS7, T1-2; Group 3, GS7, T3 or GS8-10, T1-2; Group 4, GS8-10, T3.

\(^c\)RTOG: Radiation Therapy Oncology Group [29].

often employed as a sole treatment, or it is used following incomplete resection. However, these tumors are generally radio-resistant and the effect of photon radiation is not sufficient for long-term control. For fast neutrons, reviews of published series are highly suggestive of a therapeutic advantage but in many reports the incidence of severe toxicities appears unacceptably high [30]. In this sense, C-ion RT, that shows higher biological effects and dose concentration than fast neutron RT, is expected to be more effective against such tumors. We have demonstrated that C-ion RT could replace surgical resection in elderly patients and in patients whose function would be greatly reduced if resected, as well as provide a treatment for patients in whom resection is not an option.

Recently, due to improved operative techniques and procedures as well as pre- and postoperative treatment, the local pelvic recurrence rate of rectal cancer has been decreased, but it is still as high as 5–20%. Surgical resection has been the first choice of treatment for recurrent lesions, but they are often unresectable. However, if the recurrent lesion is successfully resected, the 5-year survival rate after resection is relatively favorable at around 30% [31]. In other words, if the local recurrent lesions can be securely controlled, a favorable prognosis may be expected, but the prognosis with RT alone is not satisfactory, with many reports describing a 50% survival period of 12 months and a 3-year survival rate of around 10% [32]. In this regard, C-ion RT is a safe and effective modality in the management of locally recurrent rectal cancer, providing good local control and offering a survival advantage with acceptable morbidities. After C-ion RT with a total dose of 73.6 GyE, the 5-year local control rate was 92.7% and the 5-year survival rate was 57.4%, both are favorably comparable to the results of surgical resection and superior to conventional RT.

In the treatment of uterine cervical cancer, mortality tends to decrease and treatment results are relatively favorable when a combination of intracavitary brachytherapy and external beam RT is used. However, the treatment results for advanced cancer are not yet satisfactory, and for this reason new therapies such as chemoradiotherapy have been indicated. C-ion RT has been used for locally advanced tumors in an attempt to reach a new breakthrough in treating tumors for which there has been little improvement in treatment results. We have demonstrated that favorable results have been obtained in C-ion RT of uterine cervical adenocarcinoma. It appears that the 5-year survival rate of 42% after C-ion RT is superior to the reported 5-year survival rates of 0–26% after standard photon therapy.

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To summarize, clinical advantages have been demonstrated in the treatment of several types of tumors with C-ion RT, in particular, non-squamous cell type of tumors including adenocarcinoma, adenoid cystic carcinoma, malignant melanoma as well as bone and soft-tissue sarcomas. Treatment of locally advanced, large tumors has also been successfully carried out with C-ions with acceptable morbidities. The physical and biological benefits of C-ions have permitted significantly shorter-course radiotherapy. C-ion RT facilities require high cost for constructing large accelerators, but this may be justified by high efficacies in cancer therapy.

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