Review

Charged particle radiotherapy at the Hyogo Ion Beam Medical Center: Characteristics, technology and clinical results

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Abstract: The Hyogo Ion Beam Medical Center was constructed in 2001 as the world’s first charged particle radiotherapy center where both proton and carbon-ion radiotherapy can be performed. From April 2001 to February 2007, more than 1,400 patients with a variety of cancers were treated. Most of the tumors except for prostate cancer were considered hard to cure with standard treatments such as surgery or conventional x-ray radiotherapy. The clinical results obtained so far are very encouraging, mainly due to the excellent dose localization to the tumor and strong cell killing effects of protons and carbon-ions. The good indications are localized tumors including skull base tumors, head and neck tumors, cancers of the lung, the liver, and the prostate, and bone and soft tissue sarcomas. Charged particle radiotherapy will significantly improve the quality of life of cancer patients and promote their speedy return to normal lives or work if it is used for early stage cancer.

Keywords: charged particle radiotherapy, protons, carbon-ions, clinical results

Introduction

Recent advances in medicine have improved the cure rate of all cancer patients to approximately 50%. In an era of 50% cancer survival rates, aggressive treatments leading to the loss of important functions or cosmetic deformations are less acceptable. Needless to say, characteristic of radiotherapy is its ability to cure cancer while preserving the patient’s normal organs and functions. However, in conventional x-ray radiotherapy, tumors cannot be selectively or locally irradiated. As a result, the radiation dose to a tumor is sometimes limited by the undesirable damage produced in normal tissues that are inevitably exposed to radiation. This is a serious limiting factor in conventional radiotherapy.

Through many years of experience, radiation oncologists have learned that in order to get better clinical results, improvement in the dose localization to a tumor is critical. There has recently been international interest in the use of charged particles, including protons and carbon-ions, in cancer therapy because they have superior dose localization compared to x-rays. In addition, carbon-ions produce an increased density of local energy deposition with high LET (linear energy transfer) components, resulting in strong cell killing effects. Accordingly, charged particle radiotherapy is considered to be at present the ideal form of radiotherapy.

In this paper, the characteristics of charged particle radiotherapy, technology and the clinical results obtained between April 2001 and February 2007 at the Hyogo Ion Beam Medical Center are reviewed.

Historical background of charged particle radiotherapy

In the over 100 year history of radiotherapy, there are two major problems which have remained unresolved. First, if a tumor is located near radiosensitive critical organs, the tumor killing dose cannot safely be delivered. The reason is that the depth dose...
of x-rays, which are widely used in current radiotherapy, decreases exponentially with an increase in the tissue depth. As a result, the integral dose to the normal tissue mostly exceeds the tumor killing dose and inevitably causes complications. Second, there are tumors which are hard to eliminate by x-rays, for example, large tumors containing a substantial number of hypoxic cells which are highly radioresistant, or tumors such as malignant melanoma or bone sarcoma which are intrinsically very radioresistant. This means that the cell killing effects of x-rays are not sufficient to eradicate these kinds of tumors. Since the beginning of radiotherapy, enormous efforts have been made to solve the two above-mentioned problems. It is no exaggeration to say that the history of radiotherapy is the history of struggling to improve the dose localization and cell killing effects of radiation.

In order to improve dose localization, Takahashi, S.\(^1\) began conformal radiotherapy in 1960. This was performed by rotating a gantry equipped with moving leaves during irradiation. The technique has greatly advanced by the use of computers and conformal radiotherapy is now widely used throughout the world. Another approach to this problem was made by Abe, M.\(^2\) who developed intraoperative radiotherapy (IORT) in 1964. The concept of IORT is based on the fact that a tumor killing dose of external beam irradiation cannot safely be given if the tumor is located near radiosensitive organs. Also, with surgery, the possibility always exists that microscopic cancer cells will be left behind even after what is believed to be a curative operation. In IORT, normal organs can be displaced out of the beam path, allowing a sterilizing dose to be safely given to surgically exposed tumors or cells that are hard to eradicate with surgery. In this way, the limiting factors of radiotherapy and surgery can simultaneously be resolved by IORT. These two innovative treatment modalities developed in Japan have greatly contributed to the improvement of dose localization to the tumor. As for the improvement in the cell killing effects of radiation, radiosensitizing compounds\(^3\) or hyperthermia\(^4\) have been developed, but the clinical results obtained so far have not been satisfactory.

On the other hand, it has been physically demonstrated in the middle of the 20\(^{th}\) century that charged particles including protons and carbon-ions have a property of forming a high dose range called a Bragg peak at arbitrary depths in tissues, and beyond the peak the dose has a sharp fall-off. Therefore, charged particles can yield a much better dose localization than x-rays. The position of the peak can be shifted by changing the beam energy and the peak is spread out by using ridge filters so that the tumor is adequately encompassed (Fig. 1). For these reasons it is assumed that a tumor can locally or selectively be irradiated if charged particles are used for radiotherapy. In addition, cell killing effects of carbon-ions were shown in an in-vitro system to be about two times stronger than x-rays due to their high LET characteristic.\(^5\) Accordingly, it is expected that both of the above mentioned limiting factors in x-ray radiotherapy will be resolved by using charged particles.

It was Wilson, R.R.\(^6\) who first realized the medical potential for excellent dose localization of protons for cancer therapy in 1946. But it took 8 years before the first patient was treated with proton beams at Lawrence Berkeley National Laboratory (LBNL) in 1954. Stimulated by the subsequent promising clinical results at Berkeley, cooperative research on the application of charged particles to radiotherapy was adopted in the U.S.-Japan Cooperative Cancer Research Program, which was started in 1974 with an agreement between the National Cancer Institute, USA and the Japan Society for Promotion of Science. Since 1983 when I was involved in this program as a principal adviser, I have promoted the plan to construct a charged particle radiotherapy facility and an accelerator to generate charged particles for medical use has been discussed between

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**Fig. 1.** Comparison of the depth dose curves of x-rays and protons.
the Japanese and U.S. groups. Scientific information, technology and materials to realize the plan have been exchanged at every meeting. Thus, cooperative clinical trials between Harvard and Tsukuba, and between Berkeley and Chiba have been developed.

Encouraged by the potential benefit of charged particle radiotherapy, the Science and Technology Agency in Japan decided to build a medical accelerator-based cancer therapy center as part of the national 10-year multi-faceted anticancer campaign, announced in 1984. Ten years later, the Heavy Ion Medical Accelerator in Chiba (HIMAC) was built at the National Institute of Radiological Sciences in Chiba. The HIMAC was the world’s only heavy ion accelerator complex dedicated to medical use and clinical research was started using carbon-ions generated by the HIMAC in June 1994.7 Then, the construction of the Hyogo Ion Beam Medical Center (HIBMC) was completed in 2001 as the world’s first facility where both proton and carbon-ion radiotherapy can be performed.8 At present, there are six particle radiotherapy facilities in Japan and six facilities in the U.S. as well. The establishment of charged particle radiotherapy is really the fruition of years of research through the U.S.-Japan Radiation Research Seminars.9

**Treatment system**

Charged particle radiotherapy at the Hyogo Ion Beam Medical Center is carried out with a comprehensive system which consists of an irradiation system, a treatment planning system and a treatment verification system.

1) **Irradiation system.** The irradiation system consists of 1. an injector system, 2. a main accelerator, 3. a high energy beam transport system, 4. a beam delivery system, 5. a patient positioning system and 6. a control system for the entire device. The injector system consists of two 10-GHz ECR ion sources; 1 MeV/u RFQ linac and 5 MeV/u Alvarez linac. The operating frequency of the linear accelerator is 200 MHz. The main accelerator is a synchrotron and its circumference is 93 m which produces protons (70–230 MeV/u) and carbon-ions (70–320 MeV/u).

There are five treatment rooms; one has a horizontal beam line, one has both horizontal and vertical beam lines, one has a 45-degree oblique beam line, and two have proton gantry lines.

To conform the Bragg peak to a target volume, the beam lines in the treatment rooms are equipped with a pair of wobbler magnets, beam scatterers, ridge filters and multi-leaf collimators.10 The ridge filter is designed to produce biologically equal effects along the spread-out Bragg peak (SOBP). The collimator is used to define the lateral contour of the target volume. The patient positioning system consists of an adjustable treatment couch, a laser pointer to adjust the patient’s position and an x-ray device in order to place the target precisely by using frontal and lateral fluoroscopy.

2) **Treatment planning system.** Treatment planning is carried out using a treatment planning system consisting of a CT, an MRI and a treatment planning device. CT and MRI images of a tumor-bearing area are loaded into the treatment planning system. These images are sent to the image fusion terminal and merged into a CT-MRI image. The clinical target volume (CTV) is drawn on the MRI part of the CT-MRI image, and the outline is transferred to the CT image. In the same way, the outlines of each organ are drawn onto the CT image. After the CTV and neighboring critical organs are drawn, the image is sent to the treatment planning terminal. The planning target volume (PTV) is then automatically drawn.

Fig. 2a shows the proton treatment planning for a patient with liver cancer (the tumor is indicated by an arrow). The dose distribution curves calculated by the treatment planning device are illustrated. As shown in this figure, the distribution is well localized
to the tumor.

3) Treatment verification system. For treatment verification, PET images are used. As charged particles produce short-lived positron-emitting isotopes in tissues, the treated site can be verified by auto-activated PET images taken immediately after irradiation using a PET camera. The positron emitters consist mainly of $^{11}$C, $^{13}$N and $^{15}$O along their trajectory induced by proton or carbon-ion beams. As the half-lives of $^{11}$C, $^{13}$N and $^{15}$O are 20.4, 10 and 2 minutes, respectively, quick transportation of a patient from the treatment room to the PET room is essential. Fig. 2b shows the CT-PET fusion image taken just after proton radiotherapy for the same patient as in Fig. 2a. The auto-activated PET image (Fig. 2b) corresponds precisely to the prescribed planning field (Fig. 2a). Radiation oncologists can thus confirm that the tumor is exactly irradiated as prescribed. It should be noted that as the intensity of activities in the PET depends on the amount of positron emitters, the activity level is not correlated to the absorbed dose of protons or carbonions. The increased auto-activated uptake in the body surface demonstrated in Fig. 2b is, therefore, considered to result presumably from a large amount of positron emitters produced in the rib. The usefulness of the PET image to verify treatment planning in proton radiotherapy was first reported from our HIBMC in 2002.$^{11}$

4) Respiratory gated irradiation system. In the treatment of patients with lung or liver cancer, the tumor moves with respiration. As a result, the margin around the tumor must be expanded so as to always irradiate it during motion. In order to concentrate the dose on a moving tumor and reduce the treatment margin, a respiratory gated irradiation technique is used. The motion of a tumor due to respiration is detected by the motion of the body surface around the chest wall. A respiratory sensor using an infrared light spot and a position-sensitive detection is placed on the abdominal wall of a patient and the respiration waveform is obtained. Protons or carbon-ions are irradiated while synchronizing with this waveform. The radiation dose to normal tissues surrounding the moving tumor can thus be minimized.

5) Patient immobilization. In order to immobilize a patient during irradiation, a fixing device using plastic materials is made for each patient. For a patient with head and neck cancer, a head fixation device with an individually shaped head rest and a facial mask is fabricated using a thermal setting plastic sheet.

6) Selection of proton or carbon-ion radiotherapy. It has widely been recognized that the relative biological effectiveness of carbon-ions is about two times higher than protons. Therefore, we generally use carbon-ions to treat tumors which are considered to be highly radioresistant. However, since there have been no randomly controlled clinical trials directly comparing proton and carbon-ion radiotherapy, we have not yet decided exact indication criteria for these two treatment modalities.

Clinical results

1) Skull base tumors. Patients with skull base tumors present a formidable management problem. Total resection is usually not possible due to involvement of normal adjacent critical structures, such as the optic nerves, cranial nerves, major blood vessels and brain stem. The adjacency of these structures also limits the radiation dose that can safely be given.

A review of the Mayo Clinic of intracranial chordoma treated by surgery with or without subsequent conventional radiotherapy reports estimated 5- and 10- year survival rates of 51% and 35%, respectively.$^{12}$ Cummings, B.J. et al.$^{13}$ reports that most patients treated with conventional radiotherapy after biopsy or incomplete resection had detectable residual chordoma present at the time of death. This is considered to result from insufficient x-ray doses delivered due to the risk of damage to neighboring important structures. As most skull base tumors have low metastatic potential, better local control may improve survival. Therefore, the objective of using charged particle radiotherapy is to improve the local control by delivering sufficient radiation doses to the tumor while minimizing exposure to the adjacent normal structures.

A total of 20 patients with skull base tumors were treated by protons ($n = 16$) or carbon-ions ($n = 4$). In proton radiotherapy, a total dose of 65 or 75 Gray equivalent (GyE)$^{12}$ was delivered in 26 or 30 fractions over 5.2 or 6.0 weeks (65 or 75 GyE/26 or 30 fr/5.2 or 6.0 w). In carbon-ion radiotherapy, a

$^{12}$ Gray equivalent dose (GyE) is defined as the proton or carbon-ion physical dose multiplied by a relative biological effect (RBE) value in order to express proton or carbon-ion doses in terms comparable to x-rays.
Table 1. Survival rates of patients with skull base tumors treated by charged particle radiotherapy

| Treatment   | Tumor histology | No. of pt.* | Overall survival rate | Follow-up period |
|-------------|-----------------|-------------|-----------------------|------------------|
| Protons     | Chordoma        | 9           | 66.7% (at 5 years)    | 6-62 months      |
|             | Chondrosarcoma  | 2           | 50.0% (at 2 years)    | 17-30 months     |
|             | Meningioma      | 2           | 100% (at 2 years)     | 20-24 months     |
|             | Angiosarcoma    | 1           | 0% (at 1 year)        | 12 months        |
|             | Epithelial tumor| 1           | 100% (at 1 year)      | 23 months        |
|             | Primitive neuro-ectodermal tumor | 1 | 100% (at 6 months) | 6 months |
| Carbon-ions | Chordoma        | 1           | 100% (at 5 years)     | 61 months        |
|             | Osteosarcoma    | 2           | 50% (at 4 months)     | 4 months         |
|             | Meningioma      | 1           | 100% (at 6 months)    | 6 months         |

*No. of pt.: number of patients

A total dose of 57.6 GyE was delivered in 16 fractions over 3.2 weeks (57.6 GyE/16 fr/3.2 w).

The clinical results of the 20 patients are summarized in Table 1. The 5-year overall survival rate of 9 patients with chordoma treated by protons is 66.7% and one patient treated by carbon-ions is alive more than 5 years with no sign of recurrence. These results are better than those obtained by surgery followed by x-ray radiotherapy.12) As for other skull base tumors, the number of patients treated is still too small to evaluate but the results obtained so far seem to be promising. Complications have been acceptable, given the major morbidity and invariably fatal outcome associated with uncontrolled tumor growth in such patients.

A representative case which accurately displays the advantage of proton radiotherapy is shown in Fig. 3. The patient was a 60-year-old female with meningioma of the cranial base, which recurred after surgical resection. Therefore, the patient received γ-knife irradiation with 18 Gy*3) in 3 fractions but still developed recurrence.(Fig.3a, b) As additional resection or conventional radiotherapy was considered to be non-beneficial, the patient was referred to the HIBMC. The patient underwent proton radiotherapy because of its potential to irradiate the tumor locally, minimizing exposure to the adjacent normal brain. The prescribed dose distribution of proton beams is shown in Fig.3c. The distribution is well localized to the tumor. MRI images taken nine months after proton radiotherapy with 65 GyE/26 fr/5.2 w show marked reduction in the tumor size (Fig.3d, e). The patient is alive with no signs of recurrence at last follow-up two years after the treatment.

From our clinical experience, charged particle radiotherapy following surgical removal of as much tumor as possible appears to represent the best management policy currently available for patients with skull base malignancies.

2) Head and neck tumors. A total of 208 patients with head and neck tumors, including those in the paranasal sinus, pharynx, parotid gland and nasal cavity were treated. One hundred and sixty seven patients were treated by protons and 41 pa-
patients were treated by carbon-ions. Most of the patients were diagnosed as inoperable or considered hard to cure with conventional x-ray radiotherapy. In proton radiotherapy, a total dose of 65 GyE/26 fr/5.2 w and in carbon-ion radiotherapy, a total dose of 57.6 GyE/16 fr/3.2 w was given.

The 5-year local control and overall survival rates of all patients were 65.9% and 37.3%, respectively. This discrepancy between the local control and the survival is considered to result from the fact that a cause of death of patients was mostly distant metastasis due to the advanced stage of their diseases. However in malignant melanoma, squamous cell carcinoma and adenocarcinoma, not only metastases but also the local failures have led to low survival rates. Of the 208 patients, clinical results of 180 patients with histopathologically proven tumors were analyzed according to the tumor histology (Table 2).

As shown in Table 2, most of the patients had locally advanced tumors (percentage of T3+T4∗ tumours was 78.3%). The 3-year local control and overall survival rates ranged from 42.9 to 100% and 23.5 to 100%, respectively, depending upon the tumor histology. The clinical results obtained are encouraging, considering that most patients had locally advanced tumors which were difficult to cure with standard treatments. An important finding is that excellent local control (92.0% at 3 years) was achieved by charged particles for adenoid cystic carcinoma which is highly resistant to x-rays.

Two representative cases are shown in Figs. 4 and 5. Fig. 4 shows a 70-year-old male with T4N0M0 gingival cancer (Fig. 4a). Histology was squamous cell carcinoma. The patient underwent proton radiotherapy. Five months after treatment, the tumor disappeared completely (Fig. 4b) and the patient is alive with no evidence of disease at the time of last follow-up three years and two months after the treatment.

Fig. 5 shows a 68-year-old male with a nasal tumor (T3N0M0). Histology was malignant melanoma (Fig. 5a). The patient underwent carbon-ion radiotherapy. Fig. 5b shows the prescribed dose distribution curves of carbon-ion beams which is sharply localized to the tumor. Fig. 5c is before treatment. The tumor was gradually reduced in size (Fig. 5d) and finally disappeared five months after the treatment (Fig. 5e). The patient is alive at last follow-up 3.5 years after the treatment.

Table 2. Local control and overall survival rates of patients with head and neck tumors treated by charged particle radiotherapy according to the tumor histology

| Histology                  | T0 | T1 | T2 | T3 | T4 | T3+T4/Total | 3 year local control | 3 year survival |
|----------------------------|----|----|----|----|----|-------------|----------------------|-----------------|
| Malig.∗ melanoma           | 2  | 7  | 14 | 24 | 10 | 34/57 (59.6%)| 42.9%                | 29.5%           |
| Squamous cell ca.†         | 1  | 1  | 3  | 13 | 25 | 38/43 (88.4%)| 46.5%                | 32.7%           |
| Adenoid cystic ca.         | 0  | 1  | 5  | 9  | 28 | 37/43 (86.0%)| 92.0%                | 80.3%           |
| Adeno ca.                  | 0  | 0  | 1  | 4  | 12 | 16/17 (94.1%)| 68.6%                | 23.5%           |
| Undiff.‡ ca.               | 0  | 0  | 2  | 2  | 7  | 9/11 (81.8%) | 100%                 | 35.7%           |
| Orfactory neuroblastoma    | 0  | 1  | 1  | 2  | 5  | 7/9 (77.8%)  | 100%                 | 100%            |

∗Malig.: Malignant, †ca.: carcinoma, ‡Undiff.: Undifferentiated

TNM: T indicates the extent of the primary tumor, N indicates the absence or presence and extent of regional lymph node metastasis, and M indicates the absence or presence of distant metastasis. The addition of numbers to these three components indicates the extent of the malignant disease.
Fig. 5. Malignant melanoma in the left nasal cavity. a: Histology, b: Dose distribution of carbon-ion beams, c: Before treatment, d: Four weeks after carbon-ion radiotherapy. The tumor was markedly reduced. e: Five months after the treatment. The tumor completely disappeared.

Table 3. Comparison between proton and carbon-ion radiotherapy in 2 year local control and overall survival rates of patients with malignant melanoma

| Treatment   | No. of patients | 2 year local control | 2 year survival |
|-------------|-----------------|----------------------|-----------------|
| Protons     | 30              | 72.3%                | 67.4%           |
| Carbon-ions | 10              | 72.3%                | 50.0%           |

Table 3 shows the comparison of effectiveness between proton and carbon-ion radiotherapy for patients with malignant melanoma in the head and neck region. From a total of 57 patients with malignant melanoma, 40 patients were selected so that the stage and tumor size distributions are comparable between the proton and carbon-ion radiotherapy groups. As shown in the table, no significant difference in therapeutic effects was found in either treatment modality.

Patients with intraoral tumors treated by charged particle radiotherapy developed oral mucositis, but the grade was significantly lower than that usually observed with x-ray radiotherapy. Therefore, all patients completed the intended treatment without interruption and were able to continue oral feeding throughout the treatment course.

As is clear from these clinical outcomes, patients with head and neck cancer are particularly well indicated for charged particle radiotherapy because of the good local control and minimum functional and cosmetic damage.

3) Lung cancer. The clinical results of conventional radiotherapy for non-small cell lung cancer (NSCLC) have remained disappointing, with a 5-year overall survival rate of about 10-30% for stages including I and II.14–16 The main reason is that the tumors are difficult to eliminate by a total dose which is tolerable to the healthy lung. In contrast, survival rates obtained by surgery for early stages are significantly better than conventional radiotherapy, with a 5-year survival rate of about 40–70% for stage I and 24-52% for stage II, respectively.17–19 Therefore, the standard treatment has been surgery for patients with resectable tumors. However, treatment of lung cancer has become a very challenging issue for radiation oncologists with the advent of highly precise radiotherapy such as stereotactic radiotherapy (SRT) and charged particle radiotherapy, which are especially suited for a precise localization of the radiation dose to the tumor.

A total of 121 patients with NSCLC were treated. The stage distribution was stage I (n = 111) and stage II (n = 10). The patients treated were those who were diagnosed as inoperable or who were not surgical candidates on the grounds of comorbidity or surgical refusal.

As the number of patients with stage II was too small to evaluate, they were excluded from the analysis and the remaining 111 patients were analyzed. Eighty five patients were treated by protons and 26 patients were treated by carbon-ions. In proton radiotherapy, a total dose of 80 GyE/20 fr/4 w or 60 GyE/10 fr/2 w, and in carbon-ion radiotherapy, a total dose of 68.4 GyE/9 fr/1.8 w was delivered.

The local control rates of 111 patients with stage I NSCLC after 2, 3, and 4 years were 92.0%, 80.2%, and 80.2%, respectively and the overall survival rates after 2, 3, and 4 years were 80.8%, 77.9%, and 57.5%, respectively. These results are comparable to those obtained by surgery and by carbon-ion radiotherapy at the National Institute of Radiological Sciences in Chiba, for which a 5-year overall survival rate of 45.3% for stage I NSCLC was reported.20 Nagata, Y. et al.21 recently published that the 3-year overall survival rates of stages IA and IB NSCLC treated by SRT were 83% and 72%, respectively. Therefore, randomized clinical trials comparing SRT and surgery with charged particle radiotherapy will be needed to evaluate not only the survival rate but also quality of life for patients with NSCLC among
these treatment modalities.

A representative case is shown in Fig. 6. The patient was a 77-year-old male with stage I NSCLC (Fig. 6a arrow). Histological examination revealed squamous cell carcinoma. The patient received proton radiotherapy with 80 GyE/20 fr/4 w. The tumor decreased in size with the progress of the treatment (Figs. 6b−d) and disappeared on a CT image taken one month after the treatment (Fig. 6e). An important finding is that PaO₂ value was not decreased by proton radiotherapy. Namely, PaO₂ before treatment was 82 mmHg, while that after treatment was 81 mmHg (Fig. 6). This suggests that respiratory function was not seriously affected by proton radiotherapy. The patient was able to return to normal life soon after the treatment and survived four years and eight months. But unfortunately the patient died of other disease.

4) Liver cancer. Prognosis of patients with hepatocellular carcinoma (HCC) is poor, with a 5-year overall survival rate of about 15%. Hepatic resection is the treatment of choice, but is restricted by its invasiveness to the liver and the patient’s poor condition. Conventional radiotherapy has played a minor role in this disease because patients can barely tolerate radiation-induced hepatitis. On the contrary, excellent dose localization of charged particle radiotherapy enables delivery of sufficient doses to the tumor, minimizing exposure to the normal liver.

Patients with HCC treated by charged particle radiotherapy were those who could not be treated effectively by operation, arterial embolization or ethanol injection. One hundred and four patients (76 male, 28 female) were treated by protons (n = 97) or by carbon-ions (n = 7). The median age was 68 years old (range 42–83 years). The stage distribution was T1 (n = 15), T2 (n = 48), T3 (n = 29) and T4 (n = 12). In proton radiotherapy, a total dose of 76 GyE/20 fr/4 w or 60 GyE/10 fr/2 w and in carbon-ion radiotherapy, a total dose of 52.8 GyE/8 fr/1.6 w, was given.

The 5-year local control and overall survival rates of the 104 patients were 86.6% and 52.2%, respectively. These results seem equivalent to those obtained by surgery, for which a cumulative survival rate of 56% at 5 years for tumors 2–5 cm in diameter was reported.22 Only a few patients experienced nausea, general fatigue or appetite loss which is commonly observed in x-ray radiotherapy for liver cancer. In some patients, a transitory increase in serum amylase level was observed, but most of the patients returned to the pretreatment level shortly after the treatment.

A representative case is shown in Fig. 7. The patient was an 81-year-old female with HCC (T2N0M0). Fig. 7a is an MRI image of this patient taken before proton radiotherapy. The tumor (arrow) was gradually reduced in size with the progress of the treatment (Fig 7b-d) and no tumor was observed on an MRI image taken three months after the treatment (Fig. 7e). The patient is alive more than five years after treatment with no evidence of disease.

Table 4 shows the comparison of effectiveness
between proton and carbon-ion radiotherapy for patients with HCC.

There was no significant difference in therapeutic effects between the two treatment modalities.

5) Prostate cancer. Radical prostatectomy has been the standard treatment for early prostate cancer. However, complications associated with the operation such as urinary incontinence or sexual dysfunction reduce the quality of life of the patient. In contrast, recent radiotherapy techniques, such as intensity-modulated radiotherapy or charged particle radiotherapy are becoming more widely used treatments because of their good local control with limited complications. In particular, charged particle radiotherapy is now playing an important role in the treatment of prostate cancer. 23, 24

A total of 669 patients with localized prostate cancer were treated. Of these, 291 patients were followed-up more than two years (median follow-up: 37 months). The clinical outcomes were analyzed for the 291 patients.

Patients were stratified according to the following criteria.

Group A (n = 170) included patients with T1 or T2a, PSA (prostate-specific antigen) < 20 ng/ml (Low risk group), Group B (n = 102) included patients with T2b or T3, PSA ≥ 20 (Intermediate risk group) and Group C (n = 19) included patients with PSA ≥ 50 irrespective of T factor (High risk group).

For Group A, a total proton dose of 74 GyE/37 fr/7.4 w was given. For Group B, hormone therapy was given before proton radiotherapy with 74 GyE/37 fr/7.4 w. For Group C, hormone therapy + proton therapy with 74 GyE/37 fr/7.4 w+ hormone therapy were given.

The 3-year overall survival rates of patients in Groups A, B, and C were 97.2%, 99.0% and 100%, respectively. PSA failure free survival rates at 3 years were 97.6% for Group A, 89.5% for Group B and 57.4% for Group C. These results appear to be equivalent to those achieved by surgery, for which the actuarial 5-year likelihood of freedom from PSA relapse rates of 91–100% and 69–87% were reported for clinical stages T1a-T1c and T2a–T2c, respectively. 25

Sexual function was well preserved and no urinary incontinence was observed in our series. Grade 2 recto-urinary toxicity (intermittent bleeding and/or moderate diarrhea) after proton radiotherapy was observed in 24 of 291 patients (8%), but these healed spontaneously and no patients needed surgical management.

6) Bone and soft tissue sarcomas. To treat bone and soft tissue tumors (B&S tumor), surgery is the treatment of choice because these tumors are in most cases highly resistant to x-rays. Recent clinical results have been greatly improved by combined therapy of surgery and chemotherapy, with 5-year survival rates of around 50–80%. However, many patients have strong opposition to surgery if it leads to cosmetic deformation or even worse amputation of the affected limbs. Charged particle radiotherapy has the potential to offer good local control without surgery due to its strong cell killing effects and excellent dose localization.

Twenty five patients with bone and soft tissue tumors were treated by proton radiotherapy (n = 10) with 65 or 75 GyE/26 or 30 fr/5.2 or 6 w, or by carbon-ion radiotherapy (n = 15) with 57.6 GyE/16 fr/3.2 w with or without chemotherapy. The tumors consisted of 12 primary B&S tumors and 13 metastatic bone tumors. Histological classification of the primary B&S tumors was osteosarcoma in three patients, chondrosarcoma in two, chordoma in two, liposarcoma in two, sarcoma in two and clinical diagnosis in one, and that of the metastatic bone tumors was renal cell carcinoma in three patients, adenocarcinoma in two, prostate cancer in one and clinical diagnosis in seven. There are 13 males and 12 females. Their age ranged from 22–81 years old, with a median of 57 years old.

The 3-year local control rate for primary B&S tumors was 100% and that for metastatic bone tumors was 77.1%. All patients are alive at last follow-up but three of the 13 patients with metastatic bone tumors are alive with disease. Although the number of patients treated is small and the follow-up period is still short, the local control achieved by charged particle radiotherapy is excellent. B&S tumors are, therefore, considered to be good candidates for this treatment as an alternative to surgery, especially when severe cosmetic deformation associated with surgery or amputation of the limb cannot be avoided.

A representative case is demonstrated in Fig. 8. The patient was a 29-year-old female with myxoid liposarcoma in the left popliteal region, which recurred after repeated surgical resections. Therefore, an orthopedic surgeon suggested that she should have the affected leg amputated. She refused and consulted the HIBMC. She received carbon-ion ra-
Table 4. Comparison between proton and carbon-ion radiotherapy in 5 year local control and overall survival rates of patients with hepatocellular carcinoma

| Treatment     | No. of patients | 5 year local control | 5 year overall survival |
|---------------|-----------------|-----------------------|-------------------------|
| Protons       | 97              | 84.5%                 | 57.4%                   |
| Carbon-ions   | 7               | 100%                  | 50.0%                   |

Fig. 8. Myxoid liposarcoma in the left popliteal region. a: Sagittal MRI image taken before treatment. The tumor is indicated by arrows. b: The axial PET image before treatment. Uptake of FDG was increased in the tumor (arrows). c: Prescribed dose distribution of carbon-ion beams. d: Histology. e: Sagittal MRI image taken five months after treatment. f: The tumor was not reduced in size but the FDG uptake was significantly decreased (arrows).

diotherapy. Fig. 8a shows the tumor (arrows) before treatment. An enhanced F-18 deoxy glucose (FDG) uptake was observed on an axial PET image corresponding to the tumor (Fig. 8b arrows). Fig. 8c shows the prescribed dose distribution, which was sharply localized to the tumor, with minimum exposure to the normal tissues surrounding the tumor. Fig. 8d shows the histology. Fig. 8e demonstrates a sagittal MRI image taken five months after the treatment. The tumor size was not reduced, but as shown in Fig. 8f, the FDG uptake was markedly decreased (arrows), which suggests a decreased glucose metabolic activity. She did not require amputation and has returned to work more than five years after the treatment with no evidence of recurrence.

Comparison of proton and carbon-ion radiotherapy

From a financial viewpoint, costs for the construction of a carbon-ion therapy facility and the running costs are about two times more expensive than proton radiotherapy. From a medical viewpoint, the cell-killing effects of carbon-ions are higher than protons. In this respect, carbon-ion radiotherapy is preferable to proton radiotherapy for the treatment of highly radioresistant tumors such as bone and soft tissue sarcomas or big tumors containing a large quantity of hypoxic cells.

From our clinical results and published reports, it seems that although the treatment time and number of fractions used in carbon-ion radiotherapy are smaller than in proton radiotherapy, there is no significant difference in controlling skull base tumors, head and neck tumors, cancers of the lung, the liver and the prostate between proton and carbon ion radiotherapy. However, since there have been no prospective, randomly controlled clinical trials directly comparing the two treatment modalities, it is impossible at present to draw any definite conclusion.

Discussion

Indications for charged particle radiotherapy are those tumors which are localized with no metastasis and are refractory to conventional radiotherapy. However, gastro-intestinal cancer is not indicated because exposure to the normal mucous membrane surrounding the tumor cannot be avoided, resulting in a high risk of radiation-induced ulceration or perforation in the worst cases.

The problem with charged particle radiotherapy is that the accelerator necessary to produce charged particles is too large to build in a hospital environment and a large amount of money (over 100 million US dollars) is necessary to construct a facility, both of which prevent the widespread use of this therapy. Therefore, the research meeting for the extension of charged particle radiotherapy (Chairman Mitsuyuki Abe) was created in 2004 under the leadership of the Ministry of Education, Culture, Sports, Science and Technology, Research Promotion Bureau, Quantum and Radiation Research Division. Various kinds of
small accelerators based on new technological innovations such as a laser-driven proton accelerator\footnote{Dosoretz, D.E., Katin, M.J., Blitzer, P.H., Rubenstein, J.H., Salenius, S., Rashid, M., Dosani, R.A., Mestas, G., Siegel, A.D. and Chadha, T.T. (1992) Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. Int. J. Radiat. Oncol. Biol. Phys. 24, 3–9.} have been proposed in these meetings. Realization of a compact accelerator will contribute to the wide use of charged particle radiotherapy in the future.

**Conclusion**

It is expected that proton or carbon-ion radiotherapy will open new horizons in the treatment of localized cancer. This is because good local control and survival, except for gastro-intestinal cancer, are possible without surgery, thereby allowing patients to return to work soon after the treatment and enabling elderly patients to enjoy a painless and useful life.

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Profile

Mitsuyuki Abe was born in 1932 in Sakata city, Yamagata prefecture. He graduated from Kyoto University, Faculty of Medicine in 1959. After a period of two years research in Germany at University of Freiburg from 1962 to 1964, he has devoted himself to the field of therapeutic radiology and oncology at Kyoto University.

In 1964 he developed a new form of radiotherapy, intraoperative radiotherapy (IORT), which was named by him. IORT is a treatment modality in which radiotherapy is performed during surgery. In IORT, normal organs can be shifted out of the beam path, allowing a sterilizing dose to be safely given to surgically exposed tumors or malignant cells that are hard to eradicate with surgery. The limiting factors of radiotherapy and surgery can thus be simultaneously resolved by IORT.
This work was published in Acta Radiologica in 1971. Abe was invited to give a lecture on IORT in the U.S. in 1975. Since then, IORT has spread in many countries in the world. In 1996 International Society of Intraoperative Radiation Therapy was founded in the U.S. and he was appointed the President of the society. The meeting is continuously held every two years. He was promoted to Professor and Chairman, Department of Radiology, Kyoto University in 1977.

Abe was awarded for his innovative IORT works, including the Philipp-Franz-von-Siebold Prize given by the President of the Federal Republic of Germany in 1983 and the Prize of the Princess Takamatsu Cancer Research Fund in 1992. He first succeeded in developing a radiofrequency hyperthermia machine for cancer therapy in 1979 and a highly precise radiotherapy planning device by using a CT, named a CT-simulator in 1987 which are now widely used in Japan. The Prize of the Minister of Science and Technology Agency, Japan was given to Abe in 1988 for these technological developments. In 1995 Abe was awarded Roentgen Medal as the 1st recipient in Asia for his pioneering and original works in the field of radiation oncology at the 100th anniversary of X-ray discovery by Wilhelm Conrad Roentgen which was held in Roentgen’s birth place Remscheid-Lennep, Germany.

He served as President in the International Society of Radiation Oncology between 1900 and 1993. His international achievements are recognized to be legion by foreign radiological societies and he was conferred many honorary degrees including Honorary Doctorate, University of Essen, Germany, Honorary Professor of Cancer Institute, Chinese Academy of Medical Sciences, Honorary Fellowship of the American College of Radiology, Honorary Fellowship of the European Society for Therapeutic Radiology and Oncology, Honorary Membership in the Radiological Society of North America and Honorary Fellowship of the Royal College of Radiologists, United Kingdom.

In 1994 he retired from Kyoto University on his appointment as Director of National Kyoto Hospital. When he retired from this post in 1998, a Hyogo prefectural governor commissioned him as President of Hyogo Medical Center for Adults to construct a charged particle radiotherapy facility in Hyogo. In 2001 the Hyogo Ion Beam Medical Center (HIBMC) was completed as the world’s first institution where both proton and carbon-ion radiotherapy can be performed. From 2006 he has participated in charged particle radiotherapy at the HIBMC as Honorary Adviser. At present he is involved in the government-based research project for the widespread use of charged particle radiotherapy by developing small accelerators based on new technological innovations such as a laser-driven proton accelerator.