Carbon Ion Radiotherapy for Unresectable Sacral Chordomas

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INTRODUCTION

Chordoma is an uncommon malignant bone tumor accounting for only 1 to 4% of all primary malignant bone tumors (1, 2). Chordomas, which arise from notochordal remnants, have slower local growth and metastasize less frequently than other bone and soft tissue malignant tumors (1, 3, 4). Sacral chordomas account for >50% of all chordomas (1–3). They are not easy to control because of their anatomic location and propensity for spreading extensively. Complete radical resection produces longer continuous local control compared with subtotal resection and an extended disease-free period (5–10). However, by the time symptoms appear, the tumor is often already so large that complete excision is frequently impossible (11). Thus, despite its low-grade malignancy, sacral chordoma has a low long-term local control rate (8, 9). Sacral chordoma also has poor sensitivity to chemotherapy (1–3). Some studies have reported that photon radiation therapy may possibly delay recurrence after incomplete resection and may also be able to relieve symptoms caused by recurrences (5, 9, 12). This study is the first report on unresectable sacral chordomas treated with charged particle carbon radiotherapy.

MATERIALS AND METHODS

Patients. Patients diagnosed with bone and soft tissue sarcomas whose tumors were judged unresectable by the referring surgeon or who had refused surgery were eligible to be registered for phase I/II or phase II carbon ion radiotherapy trial for bone and soft tissue sarcomas at the National Institute of Radiological Sciences in Chiba, Japan. In these clinical trials, patients were selected for the following reasons. Patients had no distant metastasis at the time of initial referral for treatment. Patients who had undergone prior radiation therapy at the same site were excluded. The Karnofsky performance status score is >60. The tumor had to be grossly measurable. All patients signed an informed consent form approved by the local Institutional Review Board. Details of eligibility into this trial are described in a previous article (13, 14).

Between June 1996 and August 2003, 36 lesions in 30 patients with sacral chordomas were treated with carbon ion radiotherapy in these clinical trials. All treated chordomas in these studies were defined as unresectable cases by surgeons. The study group comprised 24 men and 6 women. Mean age was 66 years (range, 41 to 85 years). Median Karnofsky performance status score was 80 (range, 70 to 90). Histopathological examination of specimens from the patients confirmed that all of the tumors were chordomas. Among the 30 patients, 23 had received no prior treatment, whereas 7 had locally recurrent tumor after previous surgical resection. Initial surgical treatment of these seven patients included cystectomy or urinary diversion, requiring skin grafts. No other treatment-related surgical interventions, including colostomy or urinary diversion, were carried out. All patients have remained ambulatory and able to stay at home after carbon ion radiotherapy.

Conclusions: Carbon ion radiotherapy is effective and safe in the management of patients with unresectable sacral chordomas and offers a promising alternative to surgery.

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of two patients were postoperative recurrences and located in other intrapelvic areas. Six patients who developed metastases after initial carbon ion radiotherapy received additional carbon ion radiotherapy to the site of their metastases. All patients were followed regularly for at least 9 months. However, two metastases were followed for <6 months after they were treated with salvage carbon ion radiotherapy: the remaining 34 lesions were followed at least 9 months after carbon ion radiotherapy. Characteristics of the 30 study patients are summarized in Table 1.

**Carbon Ion Radiotherapy.** The specific technique of carbon ion radiotherapy used at National Institute of Radiological Sciences has been described in detail in previous publications (13–20). The Heavy Ion Medical Accelerator in Chiba generates carbon ion beams. The accelerated energies of the carbon ion beam are 290, 350, and 400 MeV/n. The range of these energy beams is a depth of 15 to 25 cm in water. The patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic sheet. A set of computed tomography (CT) images of 5-mm slice thickness were taken for treatment planning. Respiratory gating of both the CT acquisition and the therapy were performed when indicated (15). Three-dimensional treatment planning of carbon ion radiotherapy was performed using the software HIPLAN (National Institute of Radiological Sciences, Chiba, Japan; ref. 16). The planning target volume included the clinical target volume plus a 5-mm safety margin for positioning errors. Tumor spreading was evaluated by magnetic resonance imaging, CT, and positron emission tomography. In cases where the tumor was located close to critical organs such as the bowel, the margin was reduced accordingly. The clinical target volume was covered by at least 90% of the prescribed dose. We used dosages from 52.8 GyE [carbon physical dose (Gy) × relative biological effectiveness] to 73.6 GyE on the basis of the trials of bone and soft tissue tumor (13, 14). Relative biological effectiveness was evaluated by both radiobiological and physical studies (17, 18). Carbon ion radiotherapy was performed once a day, 4 days a week (Tuesday to Friday), for a total of 16 fixed fractions over 4 weeks. Two to four irregularly shaped ports were applied. One port was treated in each session. At every treatment session, the

<table>
<thead>
<tr>
<th>No</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Tumor volume (cm³)</th>
<th>Tumor extension</th>
<th>Dose (GyE)</th>
<th>Surgery</th>
<th>Duration of local failure (mos)</th>
<th>Duration of metastases (mos)</th>
<th>Metastatic site</th>
<th>Salvage therapy</th>
<th>Survival</th>
<th>Follow-up period (mos)</th>
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</tbody>
</table>

Abbreviations: CIRT, carbon ion radiotherapy; AWD, alive with disease; DID, dead of intercurrent disease; DOD, dead of disease; CDF, continuous disease free.

* One died of gastric cancer.
† Two died of pneumonia.
‡ Three died of brain hemorrhage.
position was confirmed with a computer-aided, on-line positioning system.

Most patients had large tumors occupying the whole pelvis. Mean clinical target volume of all lesions was 544 cm$^3$ (range, 25 to 1468 cm$^3$), and mean clinical target volume of the first treatment sites was 610 cm$^3$ (range, 260 to 1468 cm$^3$). Twenty-five lesions received a total dose of 70.4 GyE and 8 other lesions received 73.6 GyE. One huge tumor was divided into two fields because it was spreading into the right and left gluteus muscles.

Statistics. Patients have been closely followed with physical examinations, CT, and magnetic resonance imaging. Initial follow-up examinations were performed 1 to 2 months after the completion of carbon ion radiotherapy, after which, examinations were performed every 3 to 6 months. The follow-up period was calculated from the initial date of carbon ion irradiation. Recurrence was defined as tumor regrowth, i.e., an increase in tumor volume observed in two consecutive magnetic resonance imaging or CT scans. The mode of failure was defined as follows in this study: local failure, if a relapse was within the planning target volume; a relapse within distance of 2 cm was considered marginal; and if a tumor growth was found >2 cm apart from the planning target volume, it was rated as a distant failure. Local control and overall survival rates were calculated by the Kaplan-Meier method using SPSS software (SPSS, Inc., Chicago, IL). The log-rank test was used for individual comparisons.

RESULTS

Tumor Response and Survival. All patients completed carbon ion radiotherapy. The median follow-up period was 30 months (range, 9 to 87 months). The 5-year local control rate was 96% (95% confidence interval, 89–100%), with only one local treatment failure inside the planning target volume (at 13 months; Fig. 1). This failure occurred with the tumor having the largest volume, 1468 cm$^3$, in our study. Most patients experienced delayed regression of tumors. Six months after carbon ion radiotherapy, 20 treated tumors had not shown any changes such as acute tumor reaction. Most of these tumors gradually regressed over the next few years (Fig. 2).

The 5-year overall survival rate was 52% (95% confidence interval, 7–97%). The 5-year cause-specific survival rate was 94% (95% confidence interval, 84–100%; Fig. 1). One patient died of local extended disease 20 months after carbon ion radiotherapy. Three patients died because of intercurrent disease without tumor recurrence: one from a brain hemorrhage at 13 months; one from gastric cancer at 56 months; and one from pneumonia at 45 months.

The incidence of distant metastasis was 23% (7 of 30 patients). The sites of distant metastasis included lung, spinal muscle, legs, lumber vertebrae, and pelvis (Table 1). The median time from the first day of carbon ion radiotherapy to the discovery of distant metastases was 29 months. Six lesions in six patients were salvaged by repeat carbon ion radiotherapy. Three lesions in two patients were treated surgically. Two patients had metastatic lesions that received no treatment. Among the seven patients with metastases, five underwent resection as initial treatment. The seven study patients with locally recurrent tumor following earlier surgery had a significantly higher incidence of distant metastases after carbon ion radiotherapy compared with the 23 patients who had received no prior treatment to carbon ion radiotherapy ($P = 0.002$).

Symptomatic Relief. Among the 30 study patients, 21 had been receiving pain medication before carbon ion radiotherapy. After carbon ion radiotherapy, the number of medicated patients decreased to 11. Among 14 patients receiving morphine or buprenorphine before or during carbon ion radiotherapy, 6 experienced reduced pain after carbon ion radiotherapy and no longer needed morphine or buprenorphine. These six patients were from the no prior treatment subgroup. Urinary dysfunction patients with incontinence before carbon ion radiotherapy experienced no improvement from carbon ion radiotherapy. However, minor urinary complaints such as frequency or urgency tended to improve after carbon ion radiotherapy. In patients with anorectal dysfunction, incontinence did not improve after carbon ion radiotherapy, but constipation was often able to be controlled by medication (Table 2). After carbon ion radiotherapy, all patients were able to walk, although some required the help of a cane. Twenty-five patients were able to perform almost
**Table 2** The number of symptomatic relief after CIRT among 23 patients with no prior treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Before CIRT (patients)</th>
<th>After CIRT (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Morphine and/or Buprenorphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<td>1</td>
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<tr>
<td>Urinary dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Dull feeling</td>
<td>7</td>
<td>4</td>
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<tr>
<td>Anorectal dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviation: CIRT, carbon ion radiotherapy.

the same life activities as just before carbon ion radiotherapy. Among the 23 cases without prior resection, 19 had improved or not changed their activity. The median Karnofsky performance score after carbon ion radiotherapy remained unchanged at 80.

**Toxicity.** Toxicity of carbon ion radiotherapy was evaluated using the National Cancer Institute Common Toxicity Criteria, version 2.0, for acute reactions. Late reactions were evaluated using the Late Effects of Normal Tissue/Subjective, Objective, Management, and Analytic scoring system in addition to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late scoring system (21, 22).

There was no case of fatal toxicity during the follow-up period after carbon ion radiotherapy. Grade 3 skin acute reactions were observed in three patients. Grade 3 skin late reactions occurred in two patients and grade 4 late skin reactions, i.e., skin grafts in two patients. No patient required a colostomy due to toxicity from carbon ion radiotherapy. One patient experienced transient grade 1 rectal bleeding 20 months after carbon ion radiotherapy. In patients with urinary dysfunction, no patient required diversion or insertion of a permanent catheter because of toxicity. Six patients had neurological complications, including temporary increase of numbness and transient incomplete paralysis of sciatic nerves.

**DISCUSSION**

Resection is generally considered to be the treatment of choice for sacral chordoma. The extent of initial surgical resection contributes to high local control rate and the prolongation of disease-free survival (5–10). Local recurrence rate is closely related to surgical margins (5). Local control rates were about 60–80% in total excision cases, compared with rates of 25–50% in subtotal resection cases (5, 7, 9). York et al. (5) demonstrated a statistically significant difference in the time from surgery to local recurrence between patients who underwent radical resection and those who underwent subtotal resection. Tumor seeding and contamination are important problems associated with surgical excision. Kaiser et al. (22) reported a 64% recurrence rate after tumor spillage versus a 28% recurrence rate without tumor spillage. Bergh et al. (10) reported that one independent prognostic factor for tumor-related death was inadequate surgical margins. Thus, although intrasosional resection is not a preferred treatment option because of the worse control of tumor and the higher relative risk of reduced survival associated with this procedure (8), the anatomic features of tumor location and spreading not infrequently result in patients having unresectable tumors or tumors that can be only incompletely resected. Indeed, reported complete or wide resection rates range from 20 to 70% in patients undergoing surgery (5–9). There are few reports concerning the follow-up history of inoperable cases. Ozaki et al. (7) reported a patient with an inoperable lesion who received radiation alone and died of the disease at 22 months. Fuller et al. (23) described two patients who received radiation alone and who died 19 and 49 months later because of local extended disease. Despite the unresectable cases in our study, we still observed a 5-year cause-specific survival rate and a 5-year local control rate of 94 and 96%, respectively.

Reported incidences of metastases range from 5 to >40% in patients with long-term follow-up (2–4). The incidence of metastases is more frequently in subtotal resection cases than complete resection cases (8). Bergh et al. (10) reported that although metastases usually appeared late in the course of disease, survival time after detection of metastases was only 0.2 years. We administered carbon ion radiotherapy to distant metastasis in six patients. All irradiated tumors were controlled during the follow-up period. Carbon ion radiotherapy seems to be feasible even after repeated resections of recurrent tumor.

Complications after surgery do occur in the treatment of sacral chordoma. In general, intensive radical resections result in greater neurological deficits than subtotal procedures (5). Extensive surgery such as total sacrectomy causes severe complications. It is difficult to avoid urinary permanent catheter and colostomy. Fatigue fracture may occur after surgery (24). In our study, among patients without prior resection, there were nine patients with tumor involvement at the S2 level, seven patients at S1, and four patients at L5. Among these patients none required a colostomy or a permanent catheter because of radiation toxicity. They remained ambulatory during and after carbon ion radiotherapy. Few studies have mentioned symptomatic relief after surgery. In higher level sacral tumors, surgical intervention was not always able to improve symptoms such as pain, inability to be ambulatory, urinary dysfunction, or bowel dysfunction. Control of sacral chordoma did not sometimes have the same meaning as improvement of activity of daily living. By contrast, among our study patients, all remained ambulatory to varying degrees, although some were unable to walk without a cane. Tumor location and pretreatment neurological status are important predictors of treatment outcome. Severe neurological deficits existing before carbon ion radiotherapy such as permanent urinary and anorectal incontinence and sciatic nerve paresis are difficult to improve.

The benefit of photon irradiation in the treatment of chordoma has been shown in several studies (1, 5, 9, 12, 23, 25). Photon irradiation after resection effectively delays local recurrence and prolongs the disease-free interval and symptomatic relief (5, 10, 12). However, overt residual tumor or unresectable tumor can rarely be cured by photon radiotherapy alone (12, 23, 25). The carbon ion beam has a superior dose distribution and higher relative biological effectiveness compared with the photon beam. The precise dose distribution offered by the carbon
ion beam enables operators to avoid radiation-induced injuries to critical organs and to apply enough doses to control tumor. The higher linear energy transfer and relative biological effectiveness of the carbon ion beam may contribute to the control of radioresistant tumor (14). In 1993, Schoenthaler et al. (26) from Lawrence Berkley Laboratory reported a 5-year local control rate of 55% in 14 postoperative patients with sacral chordomas treated by charged neon and helium particles. They applied rather high doses, 72.3 to 80.5 GyE, to tumors. However, the authors recommended maximum debulking of tumors through radical removal for tumor control. This article was the last published study about charged particle irradiation of sacral chordomas. We would postulate that the difference in outcomes between the Lawrence Berkley Laboratory study and ours resulted from the use of different charged particles, the length of the follow-up period, and the proportion of patients with prior surgical intervention. The Lawrence Berkley Laboratory study demonstrated a tendency of improved local control rate with the use of neon (high linear energy transfer) compared with helium (low linear energy transfer).

We gave high doses, 52. to 73.6 GyE, in 16 fractions over 4 weeks for this slow but locally invasive tumor. In this study, a high local control rate could be accounted for the time-dose fractionations we used. High-tech radiotherapy such as intensity modulated radiotherapy or proton therapy, which has almost similar dose conformity to carbon ion radiotherapy, might produce same results with the same time-dose fractionations. We do not yet know whether a high linear energy transfer effect of carbon ion beam influences the efficacy of carbon ion radiotherapy. A comparative study between carbon ion radiotherapy and proton therapy or intensity modulated radiotherapy using the same time-dose fractionations should be conducted to answer the question.

Patients with sacral chordomas tend to be elder at the time of diagnosis (1–4). In this study, mean age was 66 years. If the tumors locate in higher sacral levels, elderly patients face the dilemma as to whether it is better from a quality-of-life perspective to receive surgical intervention or to allow the disease to progress in its natural course without treatment. Chordomas gradually enlarge locally and spread slowly to other organs. Data from the present study indicate that carbon ion radiotherapy has efficacy against sacral chordoma and causes less toxicity than has been reported in published studies of radiotherapy to date (1, 12, 23, 25). In higher tumor levels, carbon ion radiotherapy might conclude to remain better quality-of-life after treatment than surgical intervention. Although more cases will need to be monitored over a longer period to prove the effectiveness of carbon ion radiotherapy, carbon ion radiotherapy treatment of sacral chordomas at present appears to be a promising alternative to surgery.

APPENDIX

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