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EFFECT OF CARBON ION RADIOTHERAPY FOR SACRAL CHORDOMA: RESULTS OF PHASE I-II AND PHASE II CLINICAL TRIALS

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Purpose: To summarize the results of treatment for sacral chordoma in Phase I-II and Phase II carbon ion radiotherapy trials for bone and soft-tissue sarcomas.

Patients and Methods: We performed a retrospective analysis of 38 patients with medically unresectable sacral chordomas treated with the Heavy Ion Medical Accelerator in Chiba, Japan between 1996 and 2003. Of the 38 patients, 30 had not received previous treatment and 8 had locally recurrent tumor after previous resection. The applied carbon ion dose was 52.8–73.6 Gray equivalents (median, 70.4) in a total of 16 fixed fractions within 4 weeks.

Results: The median patient age was 66 years. The cranial tumor extension was S2 or greater in 31 patients. The median clinical target volume was 523 cm^3. The median follow-up period was 80 months. The 5-year overall survival rate was 86%, and the 5-year local control rate was 89%. After treatment, 27 of 30 patients with primary tumor remained ambulatory with or without supportive devices. Two patients experienced severe skin or soft-tissue complications requiring skin grafts.

Conclusion: Carbon ion radiotherapy appears effective and safe in the treatment of patients with sacral chordoma and offers a promising alternative to surgery. © 2010 Elsevier Inc.

Carbon ion radiotherapy, charged particle therapy, clinical trials, chordoma, bone sarcoma.

INTRODUCTION

Sacral chordomas constitute >50% of all chordomas and account for only 1–4% 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). They are not easy to control because of their anatomic location and propensity for spreading extensively. Although complete radical resection produces longer continuous local control and an extended disease-free period compared with subtotal resection (4–8), by the time the symptoms first appear, chordomas are often already too large for complete excision to be possible (9, 10). Thus, despite being a low-grade malignancy, sacral chordomas have a low long-term local control rate (6, 7). Sacral chordomas also have poor sensitivity to chemotherapy (1, 2). Some studies have reported that photon radiotherapy might delay recurrence after incomplete resection and might also be able to relieve the symptoms caused by recurrence (4, 7, 9).

Carbon ion beams share certain unique physical properties with proton beams. In particular, after penetrating into the body, they emit only a low radiation dose along their travel path. They then deliver their maximal dose at the end of their range, beyond which the radiation dose decreases sharply (Bragg peak). This pattern of irradiation facilitates the delivery of an optimal radiation dose to the tumor while exposing critical organs surrounding the tumor to lower doses. In contrast, hand photon beams, including X-ray beams, apply their maximal dose near the surface of the body, and the dose decreases with an increasing depth into the body. Carbon ion radiotherapy (CIRT) can thus provide a superior dose distribution to nonsurface tumors compared with photon radiotherapy.

A distinctive property of carbon ion beams distinguishing them from proton beams is their high biologic effectiveness. Carbon ion beams deliver a larger mean energy per unit length of their trajectory (*i.e.,* greater linear energy transfer [LET]) to the body tissues than photon and proton beams.

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Furthermore, the LET of carbon ion beams increases steadily from the initial value at the entrance point as it passes through the body, reaching its maximal value at the end of its range. These advantageous treatment profiles for carbon ion beams are likely responsible for the good results with treatment of sacral chordoma, as previously reported (10).

Since 1996, we have been involved in clinical trials of CIRT for medically inoperable bone and soft-tissue sarcomas at the National Institute of Radiological Sciences, Chiba, Japan. The first Phase I-II dose-searching clinical trial was implemented between June 1996 and February 2000, followed by a Phase II fixed-dose clinical trial between April 2000 and October 2003 (11). After these trials, CIRT was approved as advanced medical technology for heavy particle radiotherapy by the Ministry of Health in Japan in October 2003.

PATIENTS AND METHODS

Patients

The patients meeting all the following eligibility criteria were registered for the Phase I-II and Phase II CIRT trials for bone and soft-tissue sarcomas: tumor deemed to be medically inoperable by the referring surgeons; no distant metastasis at the initial referral for treatment; no previous radiotherapy at the same site; a Karnofsky performance status score of >60; and a grossly measurable tumor.

All patients signed an informed consent form approved by the local institutional review board. The details of eligibility for these trials have been previously published (10–12).

Carbon ion radiotherapy

The specific technique of CIRT used at the National Institute of Radiological Sciences has been previously described in detail (10–16). The heavy ion medical accelerator in Chiba generates carbon ion beams with accelerated energies of 290 MeV/n, 350MeV/n, and 400 MeV/n. These energy beams have a range of 15–25 cm water equivalent depth. For modulation of the Bragg peak to conform to a target volume, the beam lines for treatment are equipped with a pair of wobbler magnets, beam scatterers, ridge filters, multileaf collimators, and compensation bolus. The ridge filter is designed to produce biologically equal effects along the spread-out Bragg peak. The energies of 350 and 400 MeV/n are used mainly for treatment of sacral chordomas.

The patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic sheet. A series of computed tomography (CT) images with a 5-mm slice thickness was taken for treatment planning. Respiratory gating for both CT acquisition and therapy was performed when indicated (13, 14). We began applying respiratory gating because we had observed moving skin lines on the planning CT images.

Three-dimensional treatment planning of CIRT was performed using the HIPLAN software program (National Institute of Radiological Sciences, Chiba, Japan) (15, 16). The planning target volume (PTV) included the clinical target volume plus a 5-mm safety margin for positioning errors. The tumor extent was evaluated by magnetic resonance imaging, CT, and positron emission tomography. In cases in which the tumor was located close to critical organs, such as the bowel, the margin was reduced accordingly.

The clinical target volume was covered by ≥90% of the prescribed dose (Fig. 1). We used dosages of 52.8–73.6 Gray equivalents (GyE) (carbon physical dose in Gray × relative biologic effectiveness [RBE]) on the basis of the results from previous trials of bone and soft-tissue tumors (10, 11). The RBE was evaluated using both radiobiologic and physical studies (15, 16). CIRT was performed once daily, 4 d/wk (Tuesday to Friday), for a total of 16 fixed fractions within 4 weeks. Two to four irregularly shaped ports were applied. One port was treated in each session. At every treatment session, patient positioning was confirmed with a computer-aided, on-line positioning system. The median clinical target volume of the tumors was 523 cm^3 (range 135–1,468). Of the 38 patients, 1 received a total dose of 54.8 GyE, 1 a dose of 64.0 GyE, 29 a dose of 70.4 GyE, and 7 received a total dose of 73.6 GyE. One huge tumor was divided into two fields because it was spreading into the right and left gluteus muscles.

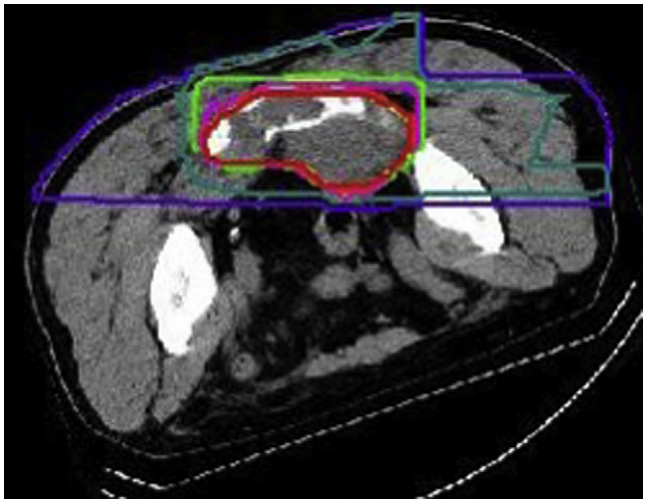

Fig. 1. Dose distribution of carbon ion beams in sacral chordoma. Red line represents 90% isodose of prescribed dose 70.4 GyE using three ports.

Statistical analysis

The patients were closely monitored through physical examinations, CT, and magnetic resonance imaging. The initial follow-up examinations were performed at the end of CIRT and again 1–2 months after CIRT completion. We planned subsequent follow-up visits to check the progress of our patients at our hospital at least every 6 months. However, for some patients, who were elderly or lived in remote places, our only recourse was to estimate their condition using imaging films taken at local hospitals and the medical reports from their local doctors.

The follow-up period was calculated from the initial date of CIRT. Recurrence was defined as tumor regrowth (*i.e.,* an increase in tumor volume observed on two consecutive magnetic resonance imaging or CT scans). The mode of failure in the present study was defined as follows: local failure, relapse within the PTV; marginal failure, relapse within 2 cm of the PTV; and distant failure, tumor growth identified >2 cm from the PTV.

The local control and overall survival rates were calculated using the Kaplan-Meier method. The log–rank test was used for individual comparisons. The last follow-up date was August 2008, with the exception of 1 patient who had not been located for 34 months after treatment.

RESULTS

Between June 1996 and October 2003, 39 patients with sacral chordoma were registered for the trials. After registration, 1 patient was excluded from analysis because only