 Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull

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Sixty-eight patients with chordoma or low-grade chondrosarcoma at the base of the skull received fractionated high-dose postoperative radiation delivered with a 160-MeV proton beam. Protons have favorable physical characteristics which allow the delivery of high doses of radiation to these critically located tumors. The methods employed for these treatments are described. These patients have been followed for at least 17 months and for a median of 34 months. The median tumor dose was 69 CGE (cobalt Gy equivalent): CGE is the dose in proton Gy multiplied by 1.1, which is the relative biological effectiveness for protons compared to cobalt-60. The daily dose was 1.8 to 2.1 CGE. For this group the 5-year actuarial local control rate is 82% and disease-free survival rate is 76%. The incidence of treatment-related morbidity has been acceptable.

Key Words • skull neoplasm • chordoma • chondrosarcoma • proton therapy

The management of chordomas and low-grade chondrosarcomas at the base of the skull is a complex problem. This anatomical location presents challenges for both the neurosurgeon and the radiation oncologist. Most patients receive postoperative radiation therapy in an attempt to control the often bulky residual disease. The tumors are located next to normal structures, such as the brain stem, spinal cord, temporal lobes, and optic chiasm, which can be damaged by high doses of irradiation. With conventional radiation modalities such as x-rays or cobalt-60 ($^{60}$Co) these tumors can usually be given only a moderate dose of radiation and most recur locally.

This report describes the methods and results of high-dose postoperative irradiation given primarily with a 160-MeV proton beam in 68 patients with chordoma or low-grade chondrosarcoma of the base of the skull. These patients were treated between February, 1974, and March, 1986. The first seven patients in this series were reported in 1982 by Suit, et al.

Clinical Material and Methods

Treatment Protocol

The patients were evaluated clinically, pathologically, and radiographically. All 68 patients had previously undergone biopsy or subtotal tumor removal. In every case the pathology slides were reviewed and the diagnosis was confirmed by pathologists (A.S. or A.R.) at the Massachusetts General Hospital (MGH). Computerized tomography (CT) scans were used to evaluate the extent of disease. Magnetic resonance (MR) images were also obtained in almost half of the cases. These tumors were all located in the clivus. Sites of tumor extension included the sphenoid sinus, nasopharynx, petrous bone, paraspinal regions, and the upper cervical spine.

The patients were assessed at the MGH for the feasibility of further surgery to remove additional tumor prior to beginning proton treatments. Six of the 68 patients had a second surgical procedure in order to reduce the volume of tumor. All patients had residual tumor and were without evidence of metastatic disease at the time of proton treatment.

Proton treatments were given using the 160-MeV fixed horizontal proton beam at the Harvard Cyclotron Laboratory. The physical characteristics of proton beams which make them attractive for radiation therapy are a finite range in tissue and a sharply defined lateral beam edge. These provide the basis for proton dose distributions that are superior to dose distributions obtainable with photons in certain tumor-normal tissue relationships. The base of the skull is such a situation.
The maximum depth of penetration in soft tissue for
the proton beam at the Harvard Cyclotron Laboratory
is 15.9 cm. The relative biological effectiveness of pro-
tons is 10% greater than 60Co. Dosage is expressed in
CGE (cobalt Gy equivalent units) and is determined by
multiplying the dose in proton Gy by 1.1.

Proton treatments were formulated using a comput-
erized multidimensional treatment planning system. 4,5
The seated or supine patient was immobilized in an
alpha cradle and thermoplastic face mask.* In these
positions patients moved a mean of less than 1 mm in
a 5-minute treatment interval. 3 A CT scan was per-
formed with the immobilized patient in the position for
treatment. The fixed horizontal beam necessitated treat-
ing the patient in the seated position in some cases. A
special CT scanner was used which was modified to
scan patients in either a supine or a seated position.
The slice thickness was 3 mm at 3-mm increments
through the region of the tumor.

The tumor volumes and relevant normal structures
were outlined on each slice of the treatment-planning
scan using an interactive computerized treatment-plan-
ing system. 6 This task required the use of all available
information, including radiographic and MR studies,
clinical data, and operative findings. Multiple treatment
fields for the tumor were designed to minimize the
radiation dose to adjacent critical structures, such as
the brain stem, spinal cord, optic structures, and tem-
poral lobes. 5 Brass apertures were used to shape the
edges of the fields. Lucite compensators were designed
to shape the distal end of the beam range so as to cover
just beyond the tumor. 3,24 Distributions of dose using
all treatment fields were computed on each CT slice.

Figure 1 shows a typical dose distribution in a patient
with a chordoma at the base of the skull. The volume outlined in
white shows the residual tumor after surgery. The brain stem
is outlined and the 40-CGE isodose line passes through its
center. The 50-CGE isodose line is also displayed. The
hatched area received a dose between 63 and 68 CGE. The
stippled area shows the region that received 68 CGE. The
outlined tumor is included in the 68 CGE region except in
the area adjacent to the brain stem where there was a gradient
doing dose.

Survival estimates were determined by the Kaplan-
Meier method. 11 Corresponding 95% confidence inter-
vals were calculated using Greenwood’s formula. 3 The
Mantel-Haenszel statistic (also known as the log-rank
statistic) was used to compare survival curves. 12 Prog-
nostic factors were evaluated with a stepwise backward
elimination Cox regression, with the p value for leaving
and entering the model set at 0.05. At each step the
algorithm checked that terms previously deleted were
not significant enough to reenter the model. The Statis-
tical Analysis System was used for the entire analysis.

**Patient Characteristics**

Between February, 1974, and March, 1986, 68 pa-
tients received postoperative fractionated radiation
treatment for chordoma or grade I or II chondrosar-
coma of the base of skull. In this series, 36 patients had
non-chondroid chordomas, four patients had chon-
droid chordomas (composed of an admixture of chon-
doma and malignant cartilage), and 28 patients had
low-grade chondrosarcomas. There were 33 females and
35 males. The median age was 33 years with a range
from 7 to 75 years. The median and mean follow-up pe-
Proton radiation for chordoma and chondrosarcoma of skull

The treatments were given with protons and high-energy x-rays. The proton component of the treatment ranged from 40% to 100%; most patients received 80% of the total dose with protons. High-energy x-rays were used to decrease the skin dose for a portion of the treatment and so that treatments could be administered on 5 days per week (the proton beam is available only 4 days per week). The median and mean tumor dose was 69 CGE with a range from 56.9 to 75.6 CGE. The daily dose was 1.8 to 2.1 CGE (2.1 CGE per fraction was employed in those infrequent instances when a total of four treatments were given per week). The total number of treatments ranged from 31 to 41. Sixty-four patients were treated postoperatively, and the other four patients received both preoperative and postoperative radiation. Two patients underwent a cesium-137 temporary implant at the time of operation in order to boost the dose to residual disease in the anterior ethmoid sinuses. No patient received chemotherapy.

Results

Sixty-one of the 68 patients have no evidence of active disease at the site of the original tumor. At 5 years the actuarial local control rate is 82% (95% confidence interval: 65% to 99%) (Fig. 2). Although only 11 patients have been followed for more than 5 years, the actuarial data indicate a 10-year local control rate of 58% (95% confidence interval: 26% to 90%). Seven patients have developed new neurological symptoms with an increase in tumor size on CT scans at 11 to 83 months. Of these seven patients, one had a low-grade chondrosarcoma and six had non-chondroid chordomas. Five were female and two were male. The median time to local failure was 53 months. Four of these patients are stable 2 to 36 months after further surgery for recurrent disease.

Four additional patients have had no evidence of local progression of disease but have experienced tumor growth in other locations. One patient with a chondroid chordoma suffered tumor recurrence anterior to the original lesion at 16 months after therapy. Three patients with non-chondroid chordoma developed distant disease in the lung, palate, cervical lymph nodes, and the posterior fossa. All these events took place within 4 years after treatment. The 5-year actuarial disease-free survival rate reflects all tumor recurrences and is 76% (95% confidence interval: 58% to 94%) (Fig. 3). At 10 years the actuarial disease-free survival rate is 53% (95% confidence interval: 23% to 83%).

Three patients have had visual complications. Two patients developed unilateral blindness 9 months after receiving 69 and 70 CGE, respectively, for a parasellar chondrosarcoma. Another patient experienced bilateral visual loss 34 months after receiving 67 CGE for a chordoma at the base of the skull; the chiasm received 60 CGE. This patient also had long-standing diabetes mellitus. One patient with unilateral blindness as a consequence of treatment developed a seizure disorder as well; CT showed an enhancing area in the temporal lobe which resolved on steroid therapy. In addition, nine patients have developed some degree of pituitary insufficiency and are being treated with replacement therapy.

Local control rates were compared for the three histological diagnoses (low-grade chondrosarcoma, chondroid chordoma, and non-chondroid chordoma). There were no significant differences between the groups based on the log-rank test (p = 0.17). The small number of chondroid chordomas in this series (four) does not allow a meaningful comparison of local control rates for chondroid versus non-chondroid chordomas. However, none of the four patients with chondroid chordoma have experienced local tumor recurrence.

A Cox regression analysis was performed in order to assess prognostic factors predicting local tumor recurrence. The initial model included the variables of dose, histological diagnosis, tumor volume, patient’s age and
gender, an interaction between tumor volume and gender, and the quadratic terms for age and tumor volume. The quadratic terms were included to better model the effect of age and tumor volume since both have large ranges. The final Cox regression model included tumor volume ($p = 0.01$) and an interaction between tumor volume and gender ($p = 0.02$), which indicates that females fared somewhat worse than males. As the tumor volume doubles, the relative risk of local failure increases by 3.1 for females (95% confidence interval 1.3 to 7.6). For males the relative risk of local recurrence increases by 2.2 as the tumor volume doubles (95% confidence interval: 0.9 to 5.2).

**Discussion**

Chordomas and chondrosarcomas of the base of the skull are uncommon tumors. Most reports in the literature discussing the results of surgery and radiation therapy for these tumors contain only a small number of patients. In all of these reports the radiation treatments were given using x-rays or $^{60}$Co. Cummings, et al., reported that four of 11 patients with clival chordomas were alive without symptomatologic disease at 3 1/2 to 10 years after treatment. The dose for the 11 patients ranged from 25 to 60 Gy. Perzin and Pushparaj reported on 10 patients with chordomas involving the nasopharynx and base of the skull. Five of these patients were dead because of local disease progression, four were living with progressive disease, and one was alive with local control of the tumor. Saxton reports that one of five patients with base of the skull chordoma was alive without evidence of disease at 3 years. The other four patients died due to local tumor progression. It appears that most patients treated with surgery and conventional radiation modalities ultimately die secondary to local tumor progression.

This report updates the experience reported initially by Suit, et al., and later by Rich, et al. Sixty-eight patients have received high-dose postoperative proton radiation treatments and have been followed for 17 to 152 months. The median tumor dose of 69 CGE is considerably higher than the doses reported in the literature using conventional radiation techniques. The 5-year actuarial local control rate is 82% and the disease-free survival rate is 76%. The incidence of treatment-related morbidity has been within acceptable limits. This represents a substantial gain for this group of patients.

Similar techniques have been employed at Lawrence Berkeley Laboratory where a helium ion beam was used to treat these tumors. Saunders, et al., described their initial experience. Other reports have associated the histological subtype of chordoid chordomas with a better prognosis. In our series only four patients had chordoid chordomas and hence the importance of histological type on outcome after treatment cannot be assessed. Tumor volume and patient gender were the significant prognostic factors, with small tumors and males having a better prognosis. We believe that it is important to evaluate each patient for removal of as much tumor volume as is safe prior to initiating radiation therapy.

Protons allow the delivery of high doses of radiation to chordomas and low-grade chondrosarcomas at the base of the skull following initial surgical removal. The importance of tumor volume in determining outcome after treatment emphasizes the importance of obtaining as comprehensive a surgical removal as possible. In our opinion surgical resection combined with high-dose proton radiation therapy represents the current best management for these patients.

**References**


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