Early results of ion beam radiation therapy for sacral chordoma

A Northern California Oncology Group study

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The authors report on eight patients with sacral chordoma treated with ion beam radiation therapy. Ion beams have favorable physical and biological characteristics when compared to conventional radiation therapy beams of x-rays, gamma rays, or electrons. This treatment technique has been developed to exploit those advantages. With this technique it is possible to deliver a much higher tumor dose than that usually given with conventional beams, and to date no significant normal-tissue morbidity has been noted. Seven of the eight patients currently have local control of their tumor; however, follow-up time is too short to judge the long-term local control rate of this treatment technique.

KEY WORDS • radiation therapy • ion beam therapy • helium ion • neon ion • sacral chordoma • sacrum

Chordomas are malignant neoplasms that are thought to arise from remnants of the embryonic notochord. In almost all cases they occur along the craniospinal axis, with about 50% occurring in the sacrococcygeal region, 35% in the base of the skull, and 15% in the spine. Complete resection of these tumors is often difficult due to their intimate association with critical peripheral nerves or central nervous system (CNS) structures. Patients with a chordoma are therefore frequently referred for radiation therapy following a biopsy or an incomplete resection of their tumor. However, attempts with curative high-dose radiation therapy are often contraindicated because of tumor locations near radiation-sensitive organs such as the brain stem, spinal cord, or the large or small bowel.

Chordomas can metastasize, with an incidence typically reported in the range of 10% to 25%, although in one series metastases were seen in 43% of 46 cases. The male to female ratio is 2:1, and the peak incidence is in the sixth decade of life. Chordomas are generally slow-growing tumors and can recur years after treatment. Cummings, et al., have reported on 24 patients who received radiation therapy for chordoma at the Princess Margaret Hospital, Toronto, Ontario. The survival rate at 5 years was 62%, but by 10 years this had declined to 28%, with most survivors having clinically detectable recurrence of their chordoma. These data are typical of the published results of radiation therapy for chordoma. Useful and prolonged palliation of pain and other symptoms is often achieved; however, if the patients are followed for long enough, the tumor will recur at the original site in almost all cases.

Current Radiation Technology

Some radiation oncologists believe that the high local recurrence rate is a sign that chordomas require a higher radiation dose to cure them. They therefore recommend that when these patients are to be treated with curative intent, doses of 70 Gray (Gy) or more should be given (70 Gy = 7000 rads). Cummings, et al., analyzed their results, surveyed the literature, and were unable to demonstrate improved tumor response with increasing radiation dose, although limited numbers of patients were found who had received tumor doses greater than 65 Gy. They concluded that if the dose-
cure curve for the irradiation of chordoma is the usual approximately sigmoid curve, the radiation doses in the trials reported to date must be in the region of that curve where the probability of cure is very small. That would imply that the radiation dose required to cure chordoma might be higher than the doses that can safely be delivered using conventional radiation therapy techniques. Because of this, several centers are investigating innovative radiotherapy techniques for the treatment of chordoma.

Cummings, et al.,
reported promising preliminary results using standard megavoltage therapy beams delivered in four 1-Gy treatments per day, rather than the standard single daily treatment of 2 Gy (treatments 5 days per week in both cases). Total doses ranged from 20 Gy given in 5 days to 40 Gy given in 12 days. The rationale for this regimen is that it would exploit any favorable differential between well oxygenated normal tissues and hypoxic tumor cells in their ability to repair radiation damage.3

Suit, et al.,10 from the Massachusetts General Hospital, Boston, are using a new type of radiation beam which offers superior localization of the high-dose region to the tumor, permitting high-dose irradiation of tumors located very close to critical organs such as the spinal cord. A proton beam generated by cyclotron is used. A similar program is being carried out by the University of California Lawrence Berkeley Laboratory (LBL), Berkeley, using a helium ion beam.8 Beams of protons (or any other ion) have a very favorable pattern of radiation dose with depth in tissue compared to that for conventional therapy beams of x-rays. This is because ion beams penetrate a definite and controllable distance in tissue and then stop. Most of the radiation dose is deposited in the stopping region, called the “Bragg peak.” By placing the Bragg peak on the tumor, a higher dose can be given to the tumor than to the overlying tissues, and tissues beyond the tumor receive little or no radiation.

Figure 1 is a plot of radiation dose versus depth in tissue for a conventional x-ray therapy beam and a helium ion therapy beam generated by the LBL 184-in. cyclotron. The curve for the x-ray beam shows a rapid build-up of dose just below the skin, and then an exponential fall-off in dose. To treat a tumor deep in a patient, the overlying tissues would receive a higher dose than the tumor, and tissues deep to the tumor would receive a significant dose. The curve for the helium ion beam shows a relatively low dose at the skin, a region with a very slow increase of dose with depth, an abrupt increase in dose at the Bragg peak, and a rapid fall-off in dose at the distal end of the Bragg peak. In most cases, the natural Bragg peak is too narrow to span the tumor and must be spread out to a more appropriate width. This has the effect of decreasing the height of the Bragg peak relative to the surface dose, but the pattern is still highly favorable compared to that for x-rays.

The disadvantages of the x-ray beam can often be minimized (but not eliminated) by treating the tumor from several different directions and lowering the dose reaching the normal tissues at any given tumor dose. However, this cannot be done when the tumor is very close to a vital organ, particularly if the tumor envelops the organ on two or more sides. Both Suit, et al.,10 and Saunders, et al.,6 have reported on the use of proton or helium ion beams to treat chordomas or other low-grade tumors located very close to or enveloping the brain stem or spinal cord. By exploiting the favorable dose localization characteristics of the particle beams, both groups report delivering between 70 and 80 Gy to the tumor, while keeping the nearby CNS structures at much lower doses, below the threshold doses for radiation damage to the organ. Local control rates have been good and complications uncommon, although follow-up time is short in both reports.

At LBL, beams of ions heavier than helium are also available for radiation therapy. These heavy ion beams have a favorable depth-dose pattern compared to that for x-ray beams. However, for beams of ions heavier than helium, the tissues deep to the Bragg peak do receive some radiation dose from long-range particles resulting from fragmentation of the primary beam particles. Although the physical dose localization properties
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of the heavier ion beams are degraded to some extent by this fragmentation, they do have important biological advantages compared to beams of protons, helium ions, and x-rays. The latter three beams are quite similar in terms of their effects upon tumor cells and normal tissues. It has been found that certain subsets of tumor cells are relatively resistant to irradiation with these beams (for example, hypoxic cells or cells in the late S phase of the mitotic cycle). This increased resistance is much smaller for irradiation with heavy ion beams. In addition, tumor cells are less able to repair damage from heavy ion beams than from beams of x-rays or lighter ion beams. Raju has published a good description of the biological properties of various radiation therapy beams, including ion beams. Because of these biological advantages, neon ion beams are being assessed at LBL for the therapy of tumors considered to be resistant to conventional therapy beams. In certain clinical situations, both helium and neon beams are used to optimize the treatment. This allows us to take advantage of the superior dose localization properties of the helium beam and the superior biological properties with good dose localization properties of the neon beam.

This paper reports the preliminary results of a pilot trial of helium and neon ion beam therapy for sacral chordoma which is being carried out at LBL in collaboration with the Department of Radiation Oncology, University of California, San Francisco.

Clinical Material and Methods

Between January, 1977, and June, 1984, eight patients with a sacral chordoma were treated with ion beam radiotherapy at the Lawrence Berkeley Laboratory (LBL). There were six males and two females, and the mean age at presentation was 60 years (range 39 to 69 years). The pathological material for all cases was reviewed and the diagnosis of chordoma confirmed. Computerized tomography (CT) scans were obtained for tumor localization in all cases. This was supplemented by barium enemas and bone films in some cases. In each case surgical dictations and conversations with the surgeon were used to finalize the target volume for radiation therapy. Beam entry angles, beam edge shaping, beam stopping points, and other treatment parameters were selected by the radiation oncologist using an interactive graphics-oriented computer program developed by Chen, et al., at LBL. The goal of the treatment plan was to deliver a high homogeneous radiation dose to the target volume, while keeping the dose given to nearby normal tissues and organs below the threshold dose for radiation damage.

The ion therapy beams at LBL are fixed in direction and are horizontal. Because of this, each desired beam direction for the treatment must be obtained by repositioning the patient relative to the beam, rather than by the usual technique of leaving the patient in one position (for instance, prone or supine) and rotating the treatment machine to the desired angle. In recent years, we have usually treated sacral chordoma patients with right and left lateral neon fields and a direct posterior helium field. The patient is treated from one direction daily on 4 days per week. For the lateral fields the patient is positioned supine on the treatment couch, and for the posterior field the patient is in a lateral decubitus position.

Since the radiation response of cells and tissues to ion beams is not the same as their response to conventional radiotherapy beams such as cobalt-60 gamma rays, we have elected to express our ion beam doses in terms of the equivalent dose of cobalt-60 gamma rays which would produce the same amount of cell killing. This facilitates the comparison of our treatment doses with the doses used for conventional radiotherapy treatments. We have named the dose unit the "Gray Equivalent" (GyE). For example, for a given tumor, 2 GyE given with a neon ion beam would be expected to kill the same number of cells as 2 Gy given with cobalt-60 gamma rays. For this group of patients, the daily dose selected was 2.0 to 2.25 GyE, comparable to the standard daily dose used in a conventional radiotherapy department. The protocol for this pilot study was administered jointly by the Northern California Oncology Group and the Radiation Therapy Oncology Group, Philadelphia, Pennsylvania. Informed consent was obtained from all patients after the nature of the study was fully explained.

Results of Therapy

Of the eight sacral chordoma patients treated with ion beam radiation therapy at LBL, four had the initial phase of their treatment given with conventional beams and were then referred for ion beam therapy to boost the tumor to a higher dose. Prior to radiotherapy, three patients had undergone biopsy only with no attempt at resection, two patients had had a partial resection of the tumor, and in three patients gross total removal of the tumor had been performed, with a strong suspicion of residual microscopic disease. Treatment results are summarized in Table 1.

The follow-up period is still short, ranging from 6 to 88 months and averaging 33 months. Patients are being followed with regular physical examinations and CT scans. To date, only one patient (Case 2) has had a local recurrence of the tumor. That patient's tumor did not respond to the irradiation at all and continued to grow, causing the patient's death 22 months after radiation therapy. In a second patient (Case 1) the primary tumor is controlled, but a metastasis to the mandible developed 2 years after radiotherapy. This was resected and irradiated, and the patient continues to be followed with no evidence of active tumor 88 months after her initial treatment. The other six patients are currently being followed and show no evidence of active tumor; these include three patients who had gross total excision of their tumor and who now have no sign of tumor on
TABLE 1
Results of treatment of sacral chordomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Type of Surgery*</th>
<th>Current Status</th>
<th>Survival Time (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>partial</td>
<td>no evidence of primary tumor, but distant metastasis</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>biopsy</td>
<td>died from persistent tumor</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>total</td>
<td>no evidence of tumor</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>biopsy</td>
<td>tumor shrinking</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>biopsy</td>
<td>stable</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>total</td>
<td>no evidence of tumor</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>total</td>
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<td>6</td>
</tr>
<tr>
<td>8</td>
<td>partial</td>
<td>stable</td>
<td>6</td>
</tr>
</tbody>
</table>

* Total: removal of all gross tumor, microscopic tumor left or suspected; partial: debulking of tumor; gross tumor left; biopsy: biopsy only, with no attempt at tumor debulking.

CT or physical examination. Two of the six had biopsy only of a large tumor; one of them (Case 4) has a shrinking mass 47 months after radiotherapy, and the other (Case 5) has a stable mass at 19 months. The remaining patient in this group (Case 8) had subtotal removal of the tumor, and a persistent stable mass at 6 months. There have been no serious complications. Two of the patients have prominent subcutaneous fibrosis in the presacral area; however, to date this has been asymptomatic other than slightly limiting flexion of the lumbosacral spine. There has been no gastrointestinal or genitourinary toxicity.

Tumor doses have ranged from 70 GyE to 80.5 GyE (Table 2). Treatments were given 4 days per week, and the dose for each of these daily treatments (called fractions) was generally 2.0 GyE. All patients had some or all of their treatment given with the helium ion beam. Some patients had a portion of their treatment with x-rays for logistical reasons, particularly if their home was not near LBL. In one of the patients (Case 7), an inadvertent delay between the x-ray treatment and the helium treatment resulted in prolongation of the overall treatment time. Most of the recent patients have had a portion of their treatment with the neon ion beam.

The location of sacral chordoma often precludes treatment with curative intent, since there is evidence suggesting that high radiation doses are necessary to cure this tumor. Complete surgical removal of the tumor may be impossible because of intimate association with sacral nerves. Radiation dose is limited by the proximity of the small bowel and the rectosigmoid portion of the large bowel. Ion therapy beams have favorable physical characteristics that allow higher radiation doses to be delivered to a tumor, with the same or lower doses given to nearby tissues. In addition, beams of ions heavier than helium have a biological advantage, which makes them more effective in killing tumor cells. Because of these considerations, we have started a trial of ion radiotherapy for this tumor. We have been able to deliver radiation doses greater than those usually achieved with conventional radiation therapy beams, with no major morbidity to date. There is no sign of tumor progression in seven of our eight patients. However, the mean follow-up period is only 33 months. Sacral chordoma has a propensity for recurrence long after the initial treatment, so at this time we cannot assess the long-term local control rate. The follow-up time is long enough to make us increasingly optimistic that the morbidity of the treatment is small. If so, and if we do ultimately begin to see a high rate of local recurrence, we will be able to increase the radiation dose beyond our current level of 76 to 80 GyE in an attempt to decrease the recurrence rate.

Our group has reported similar results for treatment of chordomas and other low-grade tumors near the brain stem or the spinal cord. We were able to deliver high radiation doses to tumors that were within millimeters of the cord or brain stem; in some cases, the tumor enveloped the cord on two or three sides or even surrounded it. By using a helium ion beam, we were able to irradiate the tumors to potentially curative doses of 60 to 80 GyE, while keeping the nearby critical CNS structures below the threshold dose for radiation damage. This would have been impossible with conventional radiation therapy beams.

In summary, by exploiting the favorable characteristics of ion therapy beams, we have been able to safely deliver potentially curative treatments to chordomas in...
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the base of skull, spine, and sacral regions. This report details our results in patients with sacral chordomas. Seven of the eight patients treated have no sign of tumor progression, although the follow-up time is short. We have used radiation doses higher than those usually given in standard radiotherapy practice, in the expectation that this will result in a higher tumor cure rate. To date, this has not caused any significant radiation damage to the nearby normal tissues. Our preliminary assessment, then, is that this is a promising technique for the treatment of sacral chordoma. We are therefore continuing to treat new sacral chordoma patients with ion beam radiation therapy, and are carefully monitoring the patients we have already treated. With a larger group of patients and longer follow-up of the group, we will be able to make a more definitive assessment of the efficacy of ion beam radiation therapy for sacral chordoma.

References


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