Chordomas arise from the intraosseous remnants of the notochord. They develop in the axial skeleton anywhere from the clivus to the sacrum, and they comprise 1 to 4% of primary bone tumors. Most chordomas (45–55%) occur in the sacrococcygeal region, whereas a smaller subset occurs at the base of skull (35%) or the vertebrae within the spine (10–15%). Chordomas usually occur in a patient’s fourth decade of life, but they are also found in younger and older populations. The lesions typically display a male/female sex ratio of 2:1, except for intracranial chordomas, which appear to be evenly distributed between the sexes.

Chordomas grow as expansile tumors that destroy bone. When present at the base of the skull, they often infiltrate cranial nerves and other adjacent neurological structures. Because these tumors involve normal cranial base anatomy, it can be difficult to achieve a complete resection and failure to do so usually results in regrowth of chordoma. In one series of 46 chordoma patients treated by an experienced skull base surgical team, recurrence of tumor within 5 years was demonstrated in 31% of patients. Furthermore, at least half of the patients had undergone multiple surgeries, and, as with other skull base tumors, multiple operations for recurrences can result in new neurological deficits, which ultimately affect patient quality of life. In an earlier series of 155 patients with chordoma, the authors demonstrated only a 1.5-year mean survival for patients who had undergone surgery alone compared with a 5.2-year average survival for those who had undergone surgery followed by radiotherapy. The overall long-term prognosis in this patient population is poor, with overall survival rates of 51% and 35% at 5 and 10 years, respectively, after subtotal surgery followed by radiotherapy.

Stereotactic radiosurgery has emerged as a potential treatment for some patients with chordomas either following surgery alone or surgery and radiotherapy. The steep dose gradient achievable with radiosurgery minimizes the

Abbreviations used in this paper: LINAC = linear accelerator; MR = magnetic resonance; PFS = progression-free survival.
amount of radiation that is delivered outside the tumor target. As a result, it is possible to deliver a much larger, and presumably more efficacious, dose to tumor without exceeding the radiation-related tolerance of normal tissues. In addition, several authors have hypothesized that a therapeutic gain may be achieved by treating slowly proliferating tumors, such as chordomas, with larger-sized fractions, a treatment that is only possible with radiosurgical techniques. In this report, we review our experience at Stanford University in the treatment of patients with chordomas in whom LINAC stereotactic radiosurgery was performed.

CLINICAL MATERIAL AND METHODS

Patient Population

Ten patients with cranial base or cervical chordomas underwent stereotactic radiosurgery between 1993 and 2000. The mean patient age was 49 years (range 30–73 years). There were seven men and three women. Eight patients harbored cranial base chordomas centered in the clival/petroclival region (Fig. 1). Two patients harbored cervical chordomas; one based at C-4, and the second involving C-4 and C-5 (Fig. 2). All patients had undergone at least one prior surgery, ranging from 3 weeks to 13 years prior to radiosurgical treatment. Five patients (50%) had undergone two previous surgeries whereas two patients (20%) had undergone three (Fig. 1).

Irradiation Treatments

Five patients underwent LINAC-based stereotactic radiosurgery in which we used a technique modeled after that of Winston and Lutz: computerized tomography scans were fused with MR images. Spherical treatment volumes were achieved with four noncoplanar arcs by using a 4- or 6-mV LINAC with an 80 to 100 cm source-to-axis distance. The treatment dose was selected on the basis of tumor size, location, proximity to critical neurological structures, and the number of isocenters. Multiple isocenters and arc modifications were used to approximate nonspherical tumor volumes. Arcs were also modified to minimize radiation dose to the brainstem and anterior visual pathways. The treatment dose was prescribed to the 80% isodose contour at the edge of tumor.
The CyberKnife (Accuray, Sunnyvale, CA) has been used recently for the treatment of brain tumors with complex shapes or locations that are difficult to treat using frame-based systems; to date, five patients with chordomas have been treated using this system. Instead of skeletal fixation for localization, target position is continually updated using x-ray image-to-image correlation. The precision of localization (≤ 0.3 mm) is comparable with that which can be achieved by frames, and performance with treatment fields less than 7 cm is similar to much larger medical LINACs. There are several benefits of the CyberKnife: 1) precision targeting, comparable with skeletal fixation; 2) fractionated radiosurgery of tumors adjacent to critical structures, such as the anterior visual pathways; 3) improved dosimetry by using nonisocentric treatment planning for complex nonspherical treatment volumes; and 4) radiosurgery for central nervous system tumors outside the head.

The five patients with cranial base or cervical chordomas in whom the CyberKnife was used underwent construction of an Aquaplast mask that immobilizes the head without requiring a metal stereotactic head frame. Thin-slice (1.25-mm) contrast-enhanced computerized tomography scans were then obtained and were used alone in four of the five CyberKnife-treated patients or fused with MR images in the fifth patient for treatment planning. The CyberKnife treatment planning software allows for the use of either isocentric or, in many cases, nonisocentric-based treatment planning (Fig. 2). As with frame-based radiosurgery, the treatment dose to the tumor margin is based on volume, location, and history of fractionated radiotherapy.

The treatment dose for the 10 patients varied between 18 Gy and 24 Gy (mean 19.4 Gy), which was prescribed to the 70 to 80% isodose contour at the edge of tumor. The maximum intratumoral dose ranged from 24.1 to 33.1 Gy (mean 27 Gy). Circular secondary collimators ranged in diameter from 7.5 to 20 mm (mean 14.4 mm). The tumor volume treated ranged from 1.1 to 21.5 ml. Four patients received single-fraction treatments. In one patient the tu-

Fig. 2. Case 9. Magnetic resonance images. Upper Left: Sagittal gadolinium-enhanced T1-weighted image demonstrating a C3–5 chordoma. Upper Center: Sagittal image, obtained 10 months later, revealing recurrence centered at C2–4. Upper Right: Sagittal image, obtained 2 months after the second surgery; the recurrent chordoma (arrow) was treated with CyberKnife radiosurgery. The treatment plan shows the isodose lines in sagittal (lower left), axial (lower center), and views (lower right).
mor received two fractions (18.1 Gy to 75% isodose line) because of the larger tumor volume (21.5 ml) and its proximity to the anterior visual structures. In both patients harboring cervical chordomas the lesions received 18 or 19 Gy to the tumor margin (75% isodose line) in three fractions secondary to the proximity of the spinal cord. In one patient with a clival chordoma in whom 21 Gy was delivered to the tumor margin regrowth of the tumor occurred 3 years following radiosurgery treatment; following this second subtotal resection, the patient underwent a second course of radiosurgery in three fractions of 20 Gy to a 8.5-ml volume (Table 1).

Follow-Up Course

Patients underwent clinical follow-up examination at 3 and 6 months posttreatment and then every 6 months. Neurological status was recorded and all complications were noted. Every 6 months following radiosurgery, MR images were obtained (a minimum of 3.5-mm slice thickness). These studies were used to follow the changes in size of treated chordoma and to assess for the presence of radiation-induced necrosis. Tumor size was calculated by obtaining direct measurements along three axes on follow-up MR images and comparing these with pretreatment MR imaging values. A tumor was considered to have decreased in size if it was reduced by 3 mm or greater in one or more dimensions. Tumors were considered to have increased in size if one or more dimensions were noted. Every 6 months following radiosurgery, MR images were obtained (a minimum of 3.5-mm slice thickness). These studies were used to follow the changes in size of treated chordoma and to assess for the presence of radiation-induced necrosis. Tumor size was calculated by obtaining direct measurements along three axes on follow-up MR images and comparing these with pretreatment MR imaging values. A tumor was considered to have decreased in size if it was reduced by 3 mm or greater in one or more dimensions. Tumors were considered to have increased in size if one or more dimensions were noted.

TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Location</th>
<th>No. of Isocenters*</th>
<th>Dose (Gy)</th>
<th>No. of Fractions</th>
<th>Margin Prescription Dose</th>
<th>Tumor Coverage W/I</th>
<th>No. of Coverage W/I</th>
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<tr>
<td>1</td>
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<td>2</td>
<td>24</td>
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<tr>
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<tr>
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</tr>
<tr>
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<td>1</td>
<td>18</td>
<td>1</td>
<td>93%</td>
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</tr>
<tr>
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<td>20</td>
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<tr>
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<tr>
<td>7</td>
<td>clivus</td>
<td>CyberKnife</td>
<td>20</td>
<td>3</td>
<td>95%</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>clivus</td>
<td>CyberKnife</td>
<td>18</td>
<td>1</td>
<td>91%</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>cervical spine</td>
<td>CyberKnife</td>
<td>18</td>
<td>3</td>
<td>91%</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>cervical spine</td>
<td>CyberKnife</td>
<td>19</td>
<td>3</td>
<td>95%</td>
<td></td>
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</tr>
</tbody>
</table>

* The CyberKnife uses a nonisocentric inverse treatment planning algorithm.

RESULTS

All patients were available for follow-up review, which averaged 4 years postradiosurgery (range 1–9 years). Based on our radiographic multidimensional measurement criteria, one chordoma was smaller in size (10%), seven were unchanged in size, and two had progressed (one tumor harbored by a patient who underwent reoperation and a second course of radiosurgery and the other by a patient who underwent reoperation alone). In using the recently defined Response Evaluation Criteria in Solid Tumors for determining tumor response to treatment, in which a unidimensional measurement of longest tumor diameter is used, the results were unchanged: one chordoma decreased in size during follow up, seven stabilized in size, and two progressed. With respect to clinical follow-up examination, eight patients (80%) experienced no new neurological symptoms postradiosurgery. The two patients in whom tumor progression developed (at 3 years and 2 years, respectively) after radiosurgery sustained new deficits. In the first patient new right-sided third and sixth cranial nerve palsies developed secondary to tumor growth within his right cavernous sinus; in the second a sixth cranial nerve palsy developed secondary to tumor progression. Despite reoperation and repeated radiosurgery in the first patient and reoperation alone in the second patient, the symptoms did not resolve. None of the preradiosurgery symptoms (that is, cranial nerve palsies) resolved in the other eight patients despite the provision of radiosurgery. No cases of radiation-induced necrosis or other radiation-induced complications were noted in this small series.

ILLUSTRATIVE CASES

Case 6

This 34-year-old woman presented in 1984 with sudden loss of consciousness due to hemorrhage of a previously undiagnosed posterior fossa tumor involving the left petrous bone and clivus (Fig. 1). The patient underwent an emergency craniotomy at an outside institution, and subtotal resection of a chordoma was achieved. Residual postoperative deficits included left-sided hearing loss, intermittent diplopia, and partial left facial palsy, and vocal cord paralysis. Follow up included serial MR imaging, and in 1992 a second craniotomy was performed via a retromastoid approach for a subtotal resection of the tumor. In 1998, serial MR imaging again demonstrated an increase in the size of the recurrent tumor (145% increase compared with that observed in 1996), and the patient underwent a third craniotomy via a pterional approach for debulking of the tumor. At the time of surgery, a portion of the tumor was observed to be located within the cavernous sinus. Postoperatively, the residual chordoma was treated with CyberKnife stereotactic radiosurgery.

Case 9

This 35-year-old man presented with bilateral shoulder pain. A chordoma of the cervical spine centered around C3–5 was demonstrated on sagittal gadolinium-enhanced T1-weighted MR imaging (Fig. 2 upper left). At an outside institution, the patient underwent a C-4 and C-5 corpectomy for resection of the tumor followed by anterior reconstruction and plating. Clinically, the patient’s symptoms resolved. Approximately 10 months later, the patient experienced a recurrence of symptoms, and follow-up MR imaging revealed recurrence of tumor centered at C2–4 (Fig. 2 upper center). The patient underwent a C2–5 pos-
Stereotactic radiosurgery and radiotherapy in chordomas

terior cervical laminectomy for near-total resection of tumor, followed by lateral mass plating. Two months after the second surgery, the residual chordoma (Fig. 2 upper right) was treated by frameless CyberKnife stereotactic radiosurgery. The residual tumor volume (1.1 ml) was treated with 18.5 Gy to the 75% isodose line in three fractions of 6.2 Gy to minimize radiation-induced injury to the spinal cord. A secondary collimator measuring 7.5 mm was used, and the maximum intratumoral dose was 24.7 Gy. Following the second surgery and during the 1-year follow-up period after radiosurgery, the patient continued to be symptom free.

**DISCUSSION**

Management of patients with cranial base and cervical chordomas is difficult, as a moderate to high rate of tumor recurrence and poor long-term prognosis have been demonstrated in this population. Historical treatment has generally consisted of tumor resection alone, or resection followed by radiation therapy; however, due to the extensive involvement of the cranial base or spine as well as neurological structures, complete resection is not possible in a significant subset of these patients. Furthermore, conventional radiotherapy applied in the treatment of residual or recurrent chordomas has been shown to be of benefit. 

Possible Dose Response

In several other series authors have studied patients with chordomas treated with varying doses of radiation, and a possible dose response of the radiation was revealed. Romero, et al., described 18 patients with residual postoperative chordomas who underwent radiotherapy in which a mean dose of 50.12 Gy was used; the overall actuarial 5-year survival was 38% and the 5-year PFS was 17%. They also showed that the PFS was longer for patients receiving radiation doses greater than 48 Gy when compared with those receiving doses below 40 Gy. These authors concluded that higher radiation doses increase the disease-free interval. Lybeert and Meerwaldt reviewed 18 chordoma patients, including four who underwent surgery, four who underwent conventional radiotherapy, and 10 patients who underwent surgery followed by irradiation. Analysis of their results suggested that higher radiation doses result in longer PFS and that the best long-term results can be achieved in patients who undergo surgery followed by radiotherapy. In additional studies some authors have shown that fractionated irradiation is useful in treating patients with chordomas; however, the potential for toxic doses of radiation to reach critical neurological structures can, in some instances, limit the dose delivered to the tumor itself.

Not all authors believe that there is a dose response when treating chordomas. Catton, et al., found no significant advantage to be associated with higher radiation doses when treating these tumors, a conclusion also reported by Saxton. Based on reports of 159 patients with cranial base chordomas reported in the literature, Tai et al., studied the effects of different treatment modalities. They found that while combined surgery and postoperative irradiation is preferable to either therapy alone with proton radiotherapy at Massachusetts General Hospital over an 18-year period. In 63 (31%) patients tumor progression was observed over a median follow-up period of 54 months. In 60 (95%) of the 63 patients local recurrence was demonstrated within the prior treatment site, leading the authors to conclude that local relapse is the predominant type of treatment failure for skull base chordomas. The authors emphasized the importance of aggressive combined therapy with surgery and irradiation at the time of primary treatment. O’Connell, et al., studied 62 patients with skull base chordomas treated with proton beam irradiation and concluded, similarly to Hug, et al., that residual tumor volume was a predictor of shortened overall survival following radiotherapy. Raffel, et al., reviewed 26 patients with cranial chordomas; 23 underwent conventional or heavy particle irradiation or received interstitial implants after resection. Eleven of the 26 patients died (58% survival) during the 5.6 year average follow-up period. Benk, et al., reviewed 18 children in whom photon–proton radiotherapy was used to treat skull base and cervical chordomas at the Massachusetts General Hospital. Using a median dose of 69 cGyE and a 72-month median follow up, the 5 year tumor control rate was 63% and 5-year survival rate was only 68%. The authors also showed that patients with cervical chordoma had a worse survival compared with those harboring cranial base lesions (p = 0.008).

**Conventional Radiotherapy**

Conventional radiotherapy has been used to treat chordomas for decades. Debus, et al., reported using fractionated radiotherapy to treat 45 patients with either postoperative residual chordoma or chondrosarcoma. The mean dose of radiation for chordomas was 66 Gy, and local control was 82% at 2 years and 50% at 5 years. Rich, et al., described 48 patients with chordomas who underwent conventional radiotherapy (65–70 Gy) and noted an increased survival rate over those in whom surgery alone was performed. Cummings, et al., used lower-dose of radiotherapy (40–55 Gy) but still found a survival benefit compared with surgery alone. The authors of several other series have also shown a benefit of radiotherapy in the treatment of chordomas.

**Heavy Charged Particle Radiotherapy**

In using heavy particle irradiation to treat chordomas an attempt is made to take advantage of the steeper falloff dose, which can be better achieved using this modality than with conventional radiotherapy. Hug, et al., have demonstrated in this population. Historical treatment has generally consisted of tumor resection alone, or resection followed by radiation therapy; however, due to the extensive involvement of the cranial base or spine as well as neurological structures, complete resection is not possible in a significant subset of these patients. Furthermore, conventional radiotherapy applied in the treatment of residual or recurrent chordomas has been shown to be of benefit. Cummings, et al., used lower-dose of radiotherapy (40–55 Gy) but still found a survival benefit compared with surgery alone. The authors of several other series have also shown a benefit of radiotherapy in the treatment of chordomas.

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respect to patient survival, there was no dose response when using photon irradiation. The authors, however, concluded that methods such as radiosurgery, which would allow increases in dose delivery to the target tumor without increasing morbidity, should increase tumor control.

**Stereotactic Radiosurgery**

In a select subgroup of patients with residual or recurrent chordoma stereotactic radiosurgery can be an important treatment option. The steep dose gradient achievable with radiosurgery minimizes radiation outside the tumor target, allowing the delivery of a much larger, and presumably more efficacious, dose to the tumor without exceeding the radiation-related tolerance of normal tissues. Some authors have hypothesized that a therapeutic gain may be achieved by treating slowly proliferating tumors, such as chordomas, with larger radiation doses, which is possible with radiosurgical techniques. In another study the authors showed that better postradiotherapy results were achieved when treating sacral chordomas compared with those of the cervical spine and cranial base, potentially due to the ability to deliver higher doses of radiation to the sacrum.

Muthukumar, et al., reported on 15 patients (nine with chordoma and six with chondrosarcoma) in whom gamma knife surgery was used as a follow up to an earlier study. Doses to the tumor margin were between 12 Gy and 20 Gy, and the maximum tumor dose was 24 to 40 Gy. Clinical improvement was demonstrated in eight patients, three remained stable, and four died during the average 4-year follow-up period. Of the surviving 11 patients, the tumor was reduced in size in five, had stabilized in size in five, and had increased in size in one. Miller, et al., reviewed the cases of eight patients with skull base chordoma treated with gamma knife surgery. At 2-year follow up, the authors noted a 100% local control rate and 100% patient survival rate.

**The Stanford Experience**

This study represents our experiences of treating 10 patients with chordomas who underwent LINAC radiosurgery; the average follow-up period was 4 years. From a radiological standpoint, tumor shrinkage or control was observed in 80% of patients. Despite tumor control in these eight patients, there was no significant improvement in pretreatment symptoms (that is, cranial nerve deficits). No patient developed evidence of radiation-induced necrosis following treatment, including the patient who was treated with two courses of stereotactic radiosurgery, and no other significant treatment-related morbidity was noted. In two patients radiosurgery failed to control tumor size, and one of these patients subsequently underwent repeated radiosurgery after reoperation. These treatment failures may have been caused by inadequate radiation dosage or failure to treat the entire tumor volume due to difficulty in defining tumor margin.

**Multimodality Therapy**

Resection is the initial therapy for all patients who are surgical candidates. Postresection, patients are followed clinically and radiographically, and if there is evidence of tumor recurrence, patients are considered candidates for stereotactic radiosurgery. Most patients (seven) in this series had undergone at least two prior operations, and they had sustained significant clinical deficits due to the presence of recurrent tumor as well as surgery-related morbidity. For these patients, stereotactic radiosurgery represented a noninvasive method for treating their recurrent/residual tumors. Multimodality treatment—resection followed by radiosurgery for postoperative residual chordomas—may result in a lower morbidity rate than that for patients undergoing multiple surgical procedures. It is not clear at the present time whether resection followed by radiosurgery represents a clear survival advantage over surgery followed by conventional radiotherapy.

**Role of Repeated Surgical Resection**

Not all patients with postresection tumor remnants or tumor growth are candidates for radiosurgery. As with other tumors considered for radiosurgery, chordomas larger than 3 to 3.5 cm in maximum diameter are difficult to treat without increasing radiation-related risks to the patient. Smaller-sized chordomas treated by radiosurgery may also represent a high risk if they are located adjacent to critical structures, such as the anterior visual pathways. Although the frameless CyberKnife system allows increased flexibility with respect to fractionated radiosurgical regimens, such fractionation may reduce radiation-related efficacy on the tumor. In some of these patients, repeated resection may produce more favorable results than radiosurgery. Furthermore, patients with significant chordoma-induced mass effect should not undergo radiosurgery as the likelihood of significant reduction in tumor volume following radiosurgery treatment is low.

**Potential Drawbacks of Radiosurgery**

Despite the theoretical benefits of using radiosurgery to treat chordomas, there are obvious drawbacks as well. Radiosurgery, by definition, requires precise target delineation. Although neuroimaging techniques are much improved, the anatomy of the skull base is especially complex. One may question whether modern imaging can reliably visualize the full extent of a tumor in this location, as microscopic rests of tumor may not be visible even on the best-quality MR images. Such concerns are of less importance in open resection and radiotherapy. Furthermore, despite the focused nature of radiosurgery, the close spatial relationship between many chordomas and critical brain structures inevitably results in some irradiation of nontumor tissue. Given the limited dose tolerance of many base-of-brain critical structures and the discreet spatial inaccuracies inherent in stereotactic frames, the possibility of damaging normal neurological tissue remains a risk. Additionally, given the potential slow-growing course of some chordomas, which is probably best discussed in terms of years and not months, the primary weakness of this and other published radiosurgery reports on chordomas is the relatively short follow-up period. Longer follow-up review of these patients is necessary before we can provide estimates on 5- and 10-year PFS and be certain that such tumors are completely ablated.
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CONCLUSIONS

Stereotactic radiosurgery appears to be an effective means to treat residual or recurrent chordomas following prior resection. Although our reported follow up is not as long as that documented in some series of fractionated radiotherapy and heavy charged particle irradiation, radiographically demonstrated control rates for cranial base and cervical chordomas appear to be at least comparable, if not superior, to those for photon or proton beam radiotherapy. Because radiosurgery is an outpatient procedure, minimally invasive, well tolerated, and in most cases, cost effective relative to repeated surgery, it represents a possible option for the treatment of patients with residual or recurrent chordoma following prior resection.

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References


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