Proton radiation therapy for chordomas and chondrosarcomas of the skull base

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Object. Local tumor control, patient survival, and treatment failure outcomes were analyzed to assess treatment efficacy in 58 patients in whom fractionated proton radiation therapy (RT) was administered for skull base chordomas and chondrosarcomas.

Methods. Between March 1992 and January 1998, a total of 58 patients who could be evaluated were treated for skull base tumors, 33 for chordoma and 25 for chondrosarcoma. Following various surgical procedures, residual tumor was detected in 91% of patients; 59% demonstrated brainstem involvement. Target dosages ranged from 64.8 and 79.2 (mean 70.7) Co Gy equivalent. The range of follow up was 7 to 75 months (mean 33 months).

In 10 patients (17%) the treatment failed locally, resulting in local control rates of 92% (23 of 25 patients) for chondrosarcomas and 76% (25 of 33 patients) for chordomas. Tumor volume and brainstem involvement influenced control rates. All tumors with volumes of 25 ml or less remained locally controlled, compared with 56% of tumors larger than 25 ml (p = 0.02); 94% of patients without brainstem involvement did not experience recurrence; in patients with brainstem involvement (and dose reduction because of brainstem tolerance constraints) the authors achieved a tumor control rate of 53% (p = 0.04). Three patients died of their disease, and one died of intercurrent disease. Actuarial 5-year survival rates were 100% for patients with chondrosarcoma and 79% for patients with chordoma. Grade 3 and 4 late toxicities were observed in four patients (7%) and were symptomatic in three (5%).

Conclusions. High-dose proton RT offers excellent chances of lasting tumor control and survival, with acceptable risks. In this series all small- and medium-sized tumors with no demonstrable brainstem involvement have been controlled; all such patients are alive. Surgical debulking enhanced delivery of full tumoricidal doses, but even patients with large tumors and disease abutting crucial normal structures benefited.

Key Words • chordoma • chondrosarcoma • skull base tumor • charged-particle therapy • radiation therapy • proton

Chordomas and chondrosarcomas located in the skull base are uncommon tumors and challenging to manage. Because of their location either in the clivus or petrous bone, with proximity to cranial nerves and major blood vessels, historically gross-total surgical resections were accomplished only rarely. However, rapid advancements in microsurgical resection techniques have now allowed surgeons to perform macroscopically confirmed gross-total resection in selected patients, even in areas in which resection until recently was considered inadvisable. Despite these improvements, however, many patients present with either primary or recurrent disease that is too extensive to permit gross-total resection without unacceptable risks. Because of the “piecemeal” resection technique that is required for skull base surgery, even gross-total resection often does not result in oncologically complete microscopic resection; that is, negative resection margins along the entirety of the tumor specimen are rarely accomplished. Despite the possibly long period of stability following subtotal resection, ultimately the majority of patients will experience recurrence and will die of their disease. Because the metastatic rate is relatively low (approximately 5–20%), local control of these aggressive tumors is of paramount importance.

Few reports in which the true long-term recurrence rate for these tumors is evaluated after modern, macroscopically confirmed gross-total resection are available thus far. Recurrence rates as high as 50 to 100% have been reported after conventional megavoltage x-radiation therapy, even in small lesions already treated using radical resection; local control and survival curves tend to follow a continuous downward slope. However, Suit, et al., Berson, et al., and Austin-Seymour, et al., have reported promising local control rates of 59 to 82% at 5 years; following these outcomes, patients have been increasingly treated with charged-particle radiation therapy (RT). Serial updates confirmed the earlier data and indicate that chordomas and chondrosarcomas are two distinct histological entities and that chondrosarcomas are associated with significantly better prognoses and outcomes fol-
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Following heavy-particle RT. Accordingly, soon after the establishment of the Proton Treatment Center at Loma Linda University Medical Center (LLUMC) in 1990, proton RT was used in patients who harbored skull base tumors.

In this paper we review the experience at LLUMC in treating 58 patients with chordomas and chondrosarcomas of the skull base by means of fractionated proton RT.

Clinical Material and Methods

Between March 1992 and January 1998, 60 patients underwent fractionated proton RT at LLUMC for either chondrosarcoma or chordoma of the skull base. One patient was lost to follow up 2 months after completion of RT and one patient was treated empirically for chondrosarcoma in the presence of Maffucci’s syndrome, yet without histological confirmation; both were excluded from this analysis. The present series, therefore, includes 58 patients with histologically proven chordoma or chondrosarcoma for whom serial magnetic resonance (MR) or computerized tomography (CT) studies and clinical information were available up to the time of analysis or death of the patient. The follow-up period ranged from 7 to 75 months (mean 33.2 months). The pathological specimens obtained in all 58 patients were reviewed at the time of RT, the majority (82%) by one of the authors (A.E.R.). The chondrosarcomas (25 tumors) were classified as hyaline, myxoid, or mixed hyaline and myxoid and were graded on a three-tier system. Thirty-three chordomas were evaluated for the presence or absence of chondroid areas. All tumors were found to be of low histological grade.

The patients’ age at the time of RT ranged between 10 and 85 years (mean 46.6 years) and the ratio of male to female patients was 1:1.2. Forty-four patients (76%) were referred for primary tumors, and 14 patients (24%) were treated for recurrent disease. One patient had received single-fraction radiosurgery at another facility; treatment in this individual had been directed to parts of the tumor and the patient subsequently received a full course of proton RT at our institution. Three patients (5%) were referred to us after undergoing biopsy sampling only; 40 patients (70%) were treated following one surgical resection; and 15 patients (25%) had undergone two or more (up to six) surgical procedures for tumor resection.

Both MR and CT studies were obtained in all patients before RT was administered; CT or MR studies, or both, were part of the initial diagnostic workup in all patients. If comparison of pre- and postoperative (preirradiation) images confirmed a persistent, enhancing soft-tissue lesion either within or beside the surgical resection bed, this was assumed to be evidence of gross residual disease. According to this criterion, only five patients (9%) underwent RT for presumed microscopic disease; most (91%) were treated with proton RT for macroscopic residual or recurrent tumor.

Presenting symptoms were related to the location of the tumor within the skull base. Symptoms included upper cranial nerve deficits, particularly sixth cranial nerve palsies (57%) in patients in whom tumor was located in the upper clivus or petroclival fissure, with or without gross involvement of the respective cavernous sinus. Diagnoses in patients with lower clival/occipitocervical junction lesions were based on the presence of lower cranial nerve deficits, or pain from the beginning of destruction of the occipitocervical junction. Generalized symptoms included headaches and/or nausea, and, rarely, vomiting. Patient and tumor characteristics are summarized in Table 1.

Proton RT is performed at LLUMC by using a synchrotron to accelerate and extract protons of variable energy, ranging between 155 and 200 MEV for skull base tumors. Details of the delivery system for proton RT have been reported previously.26 Four treatment rooms are available at LLUMC, including three with 360° rotating gantries and one with a fixed horizontal beam line. All patients were placed supine for treatment. At immobilization, either a custom-made mask was used or a vacuum-assisted bite block. After thin-slice contrast CT scans were obtained with the patient in the treatment position, target volumes and nontarget structures were outlined. The gross tumor volume and clinical target volume were designed according to the International Commission on Radiation Units criteria.20 Crucial normal structures such as the brainstem, upper spinal cord, both optic nerves, and the optic chiasm were delineated. The clinical target volume definition included an envelope of at least 0.5 cm around the gross tumor volume, depending on its anatomical structures and natural barriers. As a minimum, previous disease extent (tumor bed) was also included. In general, no attempt was made to include the entire surgical access route.

Treatments plans were generated using the Massachusetts General Hospital (MGH) three-dimensional (3-D) planning system, as modified by investigators at LLUMC. Digitally reconstructed radiographs were created to show the target position with respect to bone landmarks in multiple planes. Appropriate modulator wheels were selected to spread the Bragg peak. For each field, a metal aperture was created to shape the beam in cross section, as was a computer-milled wax bolus, which conformed the distal

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Chordoma</th>
<th>Chondrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>58</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>follow up (mos)</td>
<td>7–75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>33.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/M ratio</td>
<td>31:27 (1:2.1)</td>
<td>15:18 (1:1.2)</td>
<td>16:9 (1.8:1)</td>
</tr>
<tr>
<td>age (ys) at time of PRT</td>
<td>10–85</td>
<td>10–85</td>
<td>19–70</td>
</tr>
<tr>
<td>mean</td>
<td>46.6</td>
<td>48.7</td>
<td>43.7</td>
</tr>
<tr>
<td>no. of surgeries pre-PRT†</td>
<td>0–6</td>
<td>0–6</td>
<td>1–3</td>
</tr>
<tr>
<td>mean</td>
<td>1.4</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>PRT for recurrence</td>
<td>14 (24%)</td>
<td>12 (36%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>PRT for primary tumor</td>
<td>44 (76%)</td>
<td>21 (64%)</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>brainstem involvement</td>
<td>34 (59%)</td>
<td>25 (76%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>pre-PRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of patients w/ gross tumor pre-RT</td>
<td>53 (91%)</td>
<td>32 (97%)</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>tumor size at PRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to ≤15 ml</td>
<td>11 (19%)</td>
<td>3 (9%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>&gt;15 to ≤25 ml</td>
<td>11 (19%)</td>
<td>4 (12%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>&gt;25 ml</td>
<td>36 (62%)</td>
<td>26 (79%)</td>
<td>10 (40%)</td>
</tr>
</tbody>
</table>

* PRT = proton radiation therapy.
† Not including biopsy sampling only.
edge of the beam to the distal surface of the target. Orthogonal x-ray films were obtained daily to verify stereotactic alignment for each field.

Proton RT was administered once a day, 5 days per week. The proton dose was reported in units of Co Gy equivalents (CGE), which is defined as the physical proton dose multiplied by the biological effectiveness rate (relative to cobalt-60) of 1.1 (relative biological effectiveness factor).31 The dose per fraction was thus 1.8 CGE. The majority of patients (91%) received proton RT exclusively. Only six patients (10%) were treated with a combination of protons and megavoltage photons (photon component 36–50.4 Gy).

The total prescribed target doses ranged from 64.8 to 79.2 CGE (mean target dose 70.7 CGE). Dose levels to the optic nerves and optic chiasm were kept at or below 60 CGE, 64 CGE to the surface of the brainstem and spinal cord, and 53 CGE to the center of the brainstem and spinal cord. Dose-volume histograms were created for all targeted and nontargeted structures. All patients completed the full course of proton RT.

Actuarial control and survival rates were analyzed according to the Kaplan–Meier product limit method.21 Stepwise Cox proportional hazard regression analyses were performed to determine uni- and multivariate factors affecting outcome and to assess significance levels. The minimum level of significance accepted was set at probability values of 0.05 or less.8

All patients were followed up with serial MR or CT studies. Because of abundant tumor matrix in both histological types, little or no decrease in tumor size can be observed following RT.4,6,9,23,32 Therefore, local tumor control was defined as no progression of tumor-related clinical symptoms and no radiographic evidence of increase in size.6,22,32

**Results**

**Local Control and Survival**

At the time of our analysis, tumors in 48 patients (83%) remained locally controlled and in 10 patients (17%) local recurrence had been identified. Treatment in two (8%) of 25 patients with chondrosarcoma failed, resulting in local control rates of 92% (23 of 25). In comparison, eight (24%) of 33 patients with chordoma experienced progressive disease, and tumors in 25 (75%) of these patients remained locally controlled. The majority of treatment failures (seven patients) occurred within the irradiated field, either within the high-dose (four patients) or low-dose target volume (three patients). Two patients developed recurrent tumor in the soft tissues at the inferior field margins. One other patient experienced tumor growth in the nasal cavity, outside the treatment field, approximately 5 cm distant from the primary site, within the surgical

![Graph showing actuarial local tumor control following fractionated proton RT in patients with chordomas (33 patients) or chondrosarcomas (25 patients) of the skull base.](image)

**FIG. 1.** Graph showing actuarial local tumor control following fractionated proton RT in patients with chordomas (33 patients) or chondrosarcomas (25 patients) of the skull base. n.s. = not statistically significant.

**TABLE 2**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total</th>
<th>Chordoma</th>
<th>Chondrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>58</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>PRT alone</td>
<td>53 (91%)</td>
<td>31 (94%)</td>
<td>22 (88%)</td>
</tr>
<tr>
<td>combined proton/photon RT</td>
<td>6 (10%)</td>
<td>3 (9%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>RT target doses (CGE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>64.8–79.2</td>
<td>66.6–79.2</td>
<td>64.8–72</td>
</tr>
<tr>
<td>mean ± SD</td>
<td>70.7 ± 3.19</td>
<td>71.9 ± 2.93</td>
<td>69.3 ± 2.94</td>
</tr>
<tr>
<td>local failure total</td>
<td>10 of 58 (17%)</td>
<td>8 of 33 (24%)</td>
<td>2 of 25 (8%)</td>
</tr>
<tr>
<td>in-field high-dose vol (GTV)</td>
<td>4 (7%)</td>
<td>4 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>in-field low-dose vol (CTV)</td>
<td>3 (5%)</td>
<td>2 (6%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>marginal (&lt;2-cm distance from field edge)</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>failure w/in surgical access route</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alive, no tumor growth</td>
<td>49 of 58 (85%)</td>
<td>25 of 35 (71%)</td>
<td>23 of 25 (92%)</td>
</tr>
<tr>
<td>alive, tumor growth</td>
<td>6 (10%)</td>
<td>4 (11%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>died of intercurrent disease</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>died of disease</td>
<td>3 (5%)</td>
<td>3 (9%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* CTV = clinical target volume; GTV = gross tumor volume; SD = standard deviation.
access route. Thus far, no patient has developed a regional or distant metastasis. According to actuarial analysis, these data resulted in local tumor control rates of 94% at 3 years for patients with chondrosarcoma and 67% for those with chordoma. At 5 years, local control rates decreased to 75% for chondrosarcomas and 59% for chordomas, respectively. However, in view of the mean follow-up period of just 33 months, these 5-year data are still rather sensitive to solitary, late failures and additional observation time has to pass to reveal the true, long-term disease control rates. Although it was not statistically significant, a trend toward increased local tumor control was observed in patients with chondrosarcomas (p = 0.11, Fig. 1 and Table 2).

Local treatment failure resulted in the death of three patients (5%). Of the remaining six patients who are currently alive after local failure, five have evidence of locally growing disease. Despite various salvage treatments, including repeated surgical resections, attempted radiosurgery, and chemotherapy, only one patient who demonstrated local failure is currently stabilized locally. One patient has died of intercurrent disease. Overall, 54 patients (93%) are still alive. These data translate into 3- and 5-year actuarial overall survival rates of 87% and 79%, respectively, for patients with chordomas and 100% and 100%, respectively, for those with chondrosarcomas (Fig. 2 and Table 2).

Analysis of outcome according to preirradiation tumor size (gross tumor volume on the 3-D planning scan) revealed a statistically significant difference in local control probability. At 5 years, lesions in patients with gross tumor volumes of 25 ml or less remained locally controlled, compared with 56% of those with gross tumor volumes of more than 25 ml (p = 0.02). A trend was still maintained (p = 0.08) when tumor size was divided into groups (0–15 ml, 15–25 ml, and > 25 ml). Increased local control for small- and medium-sized tumors was associated with a trend toward increased overall patient survival. All patients with gross tumor volumes of 25 ml or less are currently alive at 5 years compared with 84% of those with gross tumor volumes greater than 25 ml (p = 0.18; Fig. 3 and Table 3).

Results of local control and survival analyses that took into account various characteristics of the patients, tumors, and their treatments are summarized in Table 3. Brainstem involvement, defined as tumor abutment to or varying degrees of impingement on or compression of this structure, was identified on the dose planning scan in 35 (59%) of 58 patients. In all seven patients who experienced a relapse within the radiation field, brainstem involvement was evident before the start of RT. Thus, local tumor control was significantly reduced in patients with brainstem involvement (53% compared with 94%, p = 0.04), resulting in decreased patient survival at an almost significant level (p = 0.08, Fig. 4). No significant difference in local control was noted for female compared with male patients with tumors of either histological type, although a possible trend existed in the chordoma group. With target doses exceeding 64 CGE in all patients, there was no further detectable relationship between prescribed dose and local control. Patients who had chordomas with nonchondroid features appeared to fare consistently better than did patients with chordoid chordomas, in terms of both local tumor control and survival, regardless of tumor size; however, this was a statistical trend only (p = 0.65 for local control). Treatment failure rates were evenly distributed between patients with primary as compared with recurrent disease.

**Treatment-Related Effects**

During RT and 6 weeks thereafter, all patients developed the expected side effects, which consisted of varying degrees of temporary epilation, headaches, loss of appetite, and fatigue, as well as occasional nausea and vomiting. All side effects were controlled symptomatically and no unexpected acute side effects of radiation were observed.
Chordomas arise from the remnants of the notochord. They comprise only 1 to 4% of primary bone tumors and arise within the axial skeleton, most commonly in the sacrococcygeal region (50–66%) and the skull base (approximately 35%).

Chondrosarcoma develops in any bone or secondarily in diseased bone (Paget’s disease; irradiated bone) or in a preexisting and benign cartilaginous tumor. Common sites of origin are the pelvis and femur; only 5% of tumors develop in the head and neck region.

Despite advances in microneurosurgical techniques, a histologically confirmed complete tumor resection of chordoma or chondrosarcoma in the skull base is rarely achieved and rates of tumor recurrence remain high. Accordingly, most physicians recommend adjuvant postoperative treatment. Because the results of chemotherapy have been discouraging thus far, RT remains the postoperative modality of choice. Moderately high radiation doses, such as those achieved using conventional megavoltage x-radiation techniques, have been associated with limited effectiveness. Pearlman and Friedman analyzed 73 patients (15 of their own patients and 58 identified from literature reviews) and reported a decrease in failure rates of RT associated with increasing dose levels: from 47% after less than 40 Gy, to 18% after 40 to 60 Gy, and 10% following doses in excess of 60 Gy. Pearlman and Friedman postulated the need for radiation doses greater than 70 Gy. Rich, et al., observed 13 local treatment failures in 18 patients receiving a photon dose of less than 60 Gy (local control 28%). These authors proposed dose levels of between 65 and 70 Gy, but warned of the high risk for late complications.

We observed partial pituitary insufficiency in four patients, all of whom required hormone replacement therapy, and unilateral hearing deficits in four patients, none of whom required a hearing aid. These sequelae were classified as Grade 1 and 2 effects.

**Discussion**

Chordomas arise from the remnants of the notochord. They comprise only 1 to 4% of primary bone tumors and arise within the axial skeleton, most commonly in the sacrococcygeal region (50–66%) and the skull base (approximately 35%).

Chondrosarcoma develops in any bone preformed by cartilage. It arises de novo in normal bone or secondarily in diseased bone (Paget’s disease; irradiated bone) or in a preexisting and benign cartilaginous tumor. Common sites of origin are the pelvis and femur; only 5% of tumors develop in the head and neck region.

Despite advances in microneurosurgical techniques, a histologically confirmed complete tumor resection of chordoma or chondrosarcoma in the skull base is rarely achieved and rates of tumor recurrence remain high. Accordingly, most physicians recommend adjuvant postoperative treatment. Because the results of chemotherapy have been discouraging thus far, RT remains the postoperative modality of choice. Moderately high radiation doses, such as those achieved using conventional megavoltage x-radiation techniques, have been associated with limited effectiveness. Pearlman and Friedman analyzed 73 patients (15 of their own patients and 58 identified from literature reviews) and reported a decrease in failure rates of RT associated with increasing dose levels: from 47% after less than 40 Gy, to 18% after 40 to 60 Gy, and 10% following doses in excess of 60 Gy. Pearlman and Friedman postulated the need for radiation doses greater than 70 Gy. Rich, et al., observed 13 local treatment failures in 18 patients receiving a photon dose of less than 60 Gy (local control 28%). These authors proposed dose levels of between 65 and 70 Gy, but warned of the high risk for late complications. Catton and associates recently updated their series of 45 patients and have been associated with a median overall survival time of 62 months. The median time to progression was 35 months and only approximately 20% of patients were progression free at the actuarial 5-year point. No survival advantage accrued to patients who received doses of more than 50 Gy as compared with those who received less than 50 Gy, but the authors attributed this result to patient selection.

In 1988 and 1989, investigators at the Lawrence Berkeley Laboratory (LBL) and Massachusetts General Hospital and Harvard Cyclotron Laboratory (MGH/HCL) published their first results on charged-particle RT for chordomas and chondrosarcomas of the skull base and...
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cervical spine. Berson, et al., 5 of the LBL group reported on 45 patients treated with helium or neon ions in doses ranging from 36 to 80 CGE. Sixty-two percent of patients were alive at 5 years; the actuarial local tumor control rate was 59%. A significantly higher local tumor control rate was demonstrated in patients with smaller lesions than in those with larger tumors (80% compared with 33% at 5 years). A tendency for improved local tumor control and higher survival rates was noted in patients with chondrosarcomas as compared with chordomas. Complications included three patients with unilateral loss of vision, two with blindness, and four with brainstem injury (eight [17%] of 45 patients).

Following an initial report by Suit, et al., 30 on the first 10 patients in the series, Austin-Seymour, et al., 4 analyzed 68 patients with skull base or cervical spine chordomas and chondrosarcomas and reported 82% local control and 76% disease-free survival rates at 5 years. The MGH/HCL results were updated by Munzenrider, et al., 23 who found that after radiation doses ranging from 56.8 to 75.6 CGE (median dose 68.4 CGE), the 5-year actuarial local recurrence-free survival rate was 76% and the overall survival rate was 90% for all 194 patients. With increasing patient enrollment and longer follow-up intervals, several potential prognostic factors emerged from the MGH/HCL data. A significant difference in outcome was found between patients with chordomas and chondrosarcomas, with recurrence-free survival rates of 62% compared with 95%, respectively. Female patients with chordomas fared consistently worse in both local tumor control and survival, and nonchondroid chordomas were associated with significantly improved survival rate but no improvement in local control. Grade 3 and 4 toxicities were observed in 20 patients (8%).

The difference between histological findings in chondrosarcoma and chordoma in the present series, currently only a trend, is expected to reach significance soon. With an even overall distribution of histological, treatment, and risk factors, the potential prognostic factors of female gender and chordoid subclassification now show a trend toward an unfavorable outcome.

Only a few severe proton RT–related complications have been observed to date. Recently, a couple of publications have specifically addressed the risk of late radiation injury following proton RT at MGH. For the brainstem and brain parenchyma, the mean time to expression of brainstem damage was 17 months 14 and the majority of damage to temporal lobes had manifested itself within 2 years. 52 Although some patients in our series are still within this sensitive time interval and therefore at risk, current incidence is lower than anticipated based on average tumor size and published data from the LBL and MGH/HCL series.

When a tumor abuts a critical normal structure, it will not receive the prescribed radiation dose to its entire volume. To keep the dose at an acceptable tolerance level for the brainstem, optic nerves, and optic chiasm, the dose to the tumor component in their immediate proximity will be within the gradient defined by the maximum permissible normal tissue tolerance dose and the intended prescribed target dose and, hence, is likely to be insufficient for tumor control. Austin, et al., 1 analyzed 26 patients with local tumor recurrence following proton RT at MGH/HCL and concluded, based on CT and MR review, that treatment in 75% of patients failed in regions receiving less than the prescribed dose because of normal tissue constraints. In the current series, all in-field tumor recurrences were found in patients in whom the tumor was at least abutting the brainstem at the time of proton RT. Furthermore, in a detailed review of dose planning scans in all 58 patients, including comparison of isodose distribution, dose–volume histograms, and serial follow-up scans, we identified progressive tumor growth within the region of compromised reduced radiation dose in all patients with local in-field failures. For the first time, statistical analysis in this series of patients identified brainstem involvement as a poor prognostic factor and a predictor of decreased local tumor control. This finding underlines the importance of our current practice of assessing the feasibility of additional tumor resection in these patients prior to receiving proton RT.

Salvage treatment of local relapse after proton RT is rarely successful. Sixty-three patients with recurrent tumor treated at MGH/HCL following combined photon and proton RT for skull base and cervical spine chordomas and chondrosarcomas were analyzed by Fagundes, et al. 12 Three- and 5-year survival rates have been 43% and 7%, respectively, despite various salvage procedures. Our own experience with 10 local control failures, wherein three patients died of disease, six are alive but with tumor progression, and only one patient is currently alive with stable disease, underlines the importance of optimizing proton RT. If additional tumor resection is feasible and would likely result in a significant reduction of tumor size and removal from critical, dose-limiting normal structures, that is, brainstem, optic nerve, and optic chiasm, additional surgery should be considered in preparation for proton RT. A policy of proton RT administration despite unfavorable tumor configuration or size, with surgical resection reserved for later treatment failure, cannot be supported by current data.

Patients with skull base tumors are increasingly considered candidates for stereotactic radiosurgery. Recently, Muthukumar, et al., 24 reported on 60Co gamma knife ther-
apy in 15 patients with chordomas or chondrosarcomas of the skull base. With tumor volumes ranging between 0.98 and 10.3 ml (mean 4.6 ml), doses varying from 12 to 20 Gy (median 18 Gy) were delivered to the tumor margin. In their study two patients were treated without histological confirmation of tumor type. After a median follow-up time of 40 months, two patients had died of disease, two had died of intercurrent disease, and one additional patient surviving at the time of analysis had developed tumor progression. Neither actuarial local tumor control nor actuarial survival data were presented. In our series, most tumors exceeded the sizes reportedly suitable for radiosurgery or had highly irregular configurations. However, in all 11 patients with tumor sizes smaller than 15 ml, who were thus potential candidates for stereotactic radiosurgery, the lesions remained locally controlled, as in 11 additional patients whose tumors ranged in size from 15 to 25 ml.

At present, too few reports on radiosurgery contain sufficient numbers of patients and statistical analyses to permit conclusions to be drawn about the feasibility of radiosurgery for chordomas and chondrosarcomas of the skull base. Although it is certainly appropriate to explore the role that radiosurgical techniques may have in the treatment of these tumors, results should be evaluated against the excellent outcome that can be achieved with fractionated proton RT, particularly in patients with tumors small enough and of favorable configuration and location for them to be candidates for radiosurgery.

Conclusions

Fractionated proton RT with 3-D planning allows the delivery of high radiation doses to tumors of the skull base while respecting normal tissue constraints. Relatively few significant complications have been observed, considering the high doses delivered, and given the incidence of major morbidity associated with uncontrollable tumor growth in such patients. This series convincingly establishes a link between proximity of the tumor to critical structures (brainstem), with resulting regional dose reduction, and decreased likelihood of local tumor control and patient survival. Furthermore, smaller tumor size correlated positively with improved outcome: all tumors treated within small- and medium-sized target volumes (≤ 25 ml) and without evidence of brainstem involvement remained controlled and all patients in this group are currently alive. Even in patients with unfavorable prognostic factors (large tumor size and abutment or compression of crucial normal structures) at 5 years proton RT resulted in local tumor control and survival rates in excess of 50% and 80%, respectively. Because salvage treatment of local recurrence is rarely successful, we believe that every effort should be made to ensure that maximal surgical resection is used to reduce tumor bulk in large lesions and to remove tumor from crucial normal structures. This should be done before administering high-dose proton RT. Our series confirms that the combination of optimal surgical resection, followed by high-dose proton RT, offers the best chance of tumor control and survival for the majority of patients with chordomas and chondrosarcomas of the skull base.

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