Abstract: Purpose. Our purpose was to discuss the optimal treatment and outcomes for patients with skull base chordomas.

Methods. We reviewed the pertinent literature for this study.

Results. Skull base chordomas usually arise in the clivus and are rarely completely resectable. Therefore, most are treated with radiotherapy (RT). Because of the risk of severe late complications, the dose is often limited with conventional photon RT, and the probability of cure is low. Proton RT alone or combined with photon RT (proton/photon RT) offers the advantage of improved dose distribution and the ability to treat the tumor to a higher dose without exceeding normal tissue tolerance. The 10-year local control rate after proton/photon RT is approximately 40% to 50%. The probability of local control is related to minimum tumor dose and dose inhomogeneity.

Conclusions. Skull base chordoma is a rare neoplasm that is rarely cured after surgery alone or combined with conventional RT. Proton/photon RT offers the advantage of increasing the tumor dose while minimizing the dose to normal tissues, thus reducing the risk of late complications. The optimal treatment may be photon/proton RT alone or combined with a gross total resection, when feasible. © 2005 Wiley Periodicals, Inc. Head Neck 27: 159–165, 2005

Keywords: chordomas; chondrosarcomas; proton therapy; local control; skull base; cervical spine

Epidemiology

Chordoma is a rare malignancy thought to arise from vestigial or ectopic notochord. McMaster et al reported on 400 patients with biopsy-proven chordoma from the Survival, Epidemiology, and End Results (SEER) database obtained from nine population-based cancer registries representing approximately 9.5% of the United States population from 1973 to 1995. They observed an incidence of 0.08 patients per 100,000, which was higher in men (0.10) than in women (0.06) and very uncommon in African-Americans (0.02). The age at diagnosis ranged from 3 to 95 years (median, 58.5 years) and was rarely less than 40 years (0.02 per 100,000).

Clinical Presentation

Most chordomas arise in the axial skeleton. McMaster et al reported on the following site distribution: cranial, 32%; spinal, 33%; sacral, 29%; and extra-axial or ill-defined, 6%. Cranial
presentations were more likely to occur in young patients \((p = .001)\) and women \((p = .037)\). Most skull base chordomas arise in the clivus. Noël et al\(^2\) reported on 47 patients with chordomas arising in the skull base and cervical spine and observed the following distribution: clivus, 23 patients \((49\%)\); sphenoclival, 15 patients \((32\%)\); petroclival, four patients \((9\%)\); cervical spine, three patients \((6\%)\); and other, two patients \((4\%)\). Maximum tumor diameter ranged from 1.5 to 10.0 cm \((median, 4.4 \text{ cm})\), and tumor volume ranged from 2 to 125 cm\(^3\) \((median, 21 \text{ cm}^3)\).\(^2\)

**GENETIC ALTERATIONS**

Various investigators have analyzed genetic alterations that may be involved in the genesis of chordomas. Schiel et al\(^3\) analyzed 16 chordomas from 13 patients with comparative genomic hybridization and fluorescence in situ hybridization and found, on average, 3.2 losses and 4.2 gains per tumor. The most common DNA copy number alterations were losses on 3p \((50\%)\) and 1p \((44\%)\) and gains on 7q \((69\%)\), 20q \((50\%)\), 5q \((38\%)\), and 12q \((38\%)\). The authors concluded that tumor suppressor genes or mismatch repair genes on 1p31 and 3p14 and oncogenes on 7q36 might be involved in the genesis of chordomas. Riva et al\(^4\) studied 27 patients with sporadic chordomas by means of loss of heterozygosity of 31 microsatellites localized to the 1p36.32 to 36.11 region. They detected a common molecular lesion at 1p36.13 and suggested that the CASP9, EPH2A, and DVL1 genes might play an oncosuppressing role in the development of chordomas. Kelley et al\(^5\) performed a genome-wide analysis for linkage in 22 family members; 10 of 22 had chordomas, and nine of 10 chordomas were in the skull base. The pattern of inheritance was compatible with an autosomal-dominant trait; the locus for familial chordoma was mapped to 7q33.

**NATURAL HISTORY**

Patients with chordomas often are initially seen with cranial nerve deficits (most commonly the third and sixth cranial nerves), hydrocephalus, and sensorimotor deficits.\(^2\) Volpe et al\(^6\) reported on 48 patients with skull base chordomas and observed that 52% initially were seen with ocular symptoms such as diplopia and/or visual impairment. Diplopia was often intermittent initially and was usually caused by abducens nerve palsy.

Chordomas tend to be slow growing and locally destructive; they rarely exhibit lymphatic and/or hematogenous dissemination at diagnosis. Recurrences may be observed many years after treatment, and patients may survive for several years or longer after recurrence has been detected. Figueroa et al\(^7\) reported on 204 patients with chordomas arising in the base of skull and cranial spine who were treated at Massachusetts General Hospital (Boston) between 1975 and 1993. Sixty-three patients \((31\%)\) experienced recurrent disease in the following sites: local recurrence, 49 patients \((78\%)\); regional nodal relapse, two patients \((3\%)\); surgical pathway seeding, 3 patients \((5\%)\); and/or distant metastases, 13 patients \((21\%)\). The most common sites for distant metastases were lung and bone. The 3-year and 5-year overall survival rates after relapse were 43\% and 7\%, respectively.

Haeckel et al\(^8\) analyzed 44 skull base chordomas, 10 skull base chondrosarcomas, and 10 embryo-fetal specimens containing chorda dorsalis for cathepsin K, a protease with high elastinolytic and collagenolytic activities thought to play a significant role in osteoclast-mediated bone resorption. Cathepsin K was significantly expressed in chordoma tumor cells, particularly at tumor invasion fronts, which may be related to destruction of adjacent bone by the tumor. In contrast, cathepsin K was not significantly expressed in chondrosarcoma or chorda dorsalis.

**DIAGNOSTIC EVALUATION**

The workup includes a complete history and physical examination, MRI of the primary site, and a chest roentgenogram. Because the risk of the lymphatic and/or hematogenous dissemination is low, additional studies such as a CT of the neck and/or chest are not indicated unless metastases are suspected.

Fine-needle aspiration (FNA) biopsy may be performed to establish the pathologic diagnosis. Kay et al\(^9\) reported that 14 (10\%) of 141 patients with chordoma underwent FNA at the Mayo Clinic (Rochester, MN) between 1985 and 2000; diagnostic material was present in all 14 FNAs. A core needle biopsy or open biopsy may be obtained if FNA is nondiagnostic. Open biopsy procedures may be associated with low risk of tumor seeding along the biopsy track.

**HISTOLOGIC APPEARANCE**

Chordomas may be histologically stratified into classic chordomas and chondroid chordomas; the
latter subset has a more favorable prognosis and may be confused with low-grade chondrosarcomas. Although some authors have postulated that chondroid chordomas are really chondrosarcomas, others have refuted this hypothesis. Gottschalk et al analyzed 15 classic chordomas and seven chondroid chordomas with cytoprotein expression profiling and molecular in situ localization techniques of marker gene products indicative of the developmental phenotype of chondrocytes and demonstrated that chondroid chordomas are, indeed, chordomas and not low-grade chondrosarcomas.

Because chordomas have a more unfavorable prognosis, it is important to distinguish them from low-grade chondrosarcomas. Juliao et al analyzed 16 chordomas and 12 low-grade myxoid chondrosarcomas for galectin-3, a beta-galactoside binding protein, and found that 12 (75%) of 16 chordomas stained positively for galectin-3 compared with one (8%) of 12 chondrosarcomas. Naka et al analyzed 15 chordomas and eight chondrosarcomas for cell adhesion molecules (E-cadherin, α-catenin, β-catenin, γ-catenin, and neural cell adhesion molecules) and found that all, except for α-catenin, were present significantly more often in chordomas than in chondrosarcomas (p < .05). Ishida and Dorfman analyzed the immunohistochemical staining patterns for nine patients with chondrosarcoma and seven patients with chordomas of the skull base. Chordomas were found to stain positively for epithelial membrane antigen and cytokeratin in contrast to chondrosarcomas, where these stains were likely to be negative.

The histologic appearance of chordomas may be related to proliferative activity. Naka et al evaluated chordomas in 17 patients and classified them as trabecular (eight patients) and solid (nine patients). Nuclear atypia was graded on a three-tier scale, and DNA flow cytometric and immunohistochemical techniques were used to determine proliferative activity (% S + G2 + M phase) and the MIB-1 labeling index. Immunohistochemical techniques were also used to determine p53 overexpression. Grade 2 to 3 nuclear atypia was found more often in solid chordomas than in trabecular chordomas (none of eight vs five of nine; p = .044). The proliferative index was found to be higher in grade 2 to 3 tumors. Solid chordomas tended to have a higher MIB-1 labeling index (p = .088). Two solid chordomas were found to have p53 overexpression. The MIB-1 labeling index was higher in chordomas with p53 overexpression than in those without it (p = .037).

These findings indicate that chordomas with a solid histologic pattern tend to be more likely to exhibit more nuclear atypia and have a higher proliferative index.

**STAGING**

Chordomas may be staged according to the American Joint Committee on Cancer (AJCC) staging system (Table 1). Because almost all of the skull base chordomas are T1N0, histologic grade is crucial in determining prognosis and is incorporated into the staging system.

### Table 1. American Joint Committee on Cancer Staging System, TNM Definitions.

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
<th>Stage grouping</th>
<th>Histologic grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX*</td>
<td>MX</td>
<td>T1 N0 M0 G1,2, low grade</td>
<td>GX</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
<td>T1 N0 M0 G1,2, low grade</td>
<td>G1</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>T1 N0 M0 G3,4 high grade</td>
<td>G2</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>T2 N0 M0 G3,4 high grade</td>
<td>G3</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>T3 N0 M0 Any G</td>
<td>G4</td>
</tr>
</tbody>
</table>

*Note: Because of the rarity of lymph node involvement in sarcomas, the designation NX may not be appropriate and could be considered N0 if no clinical involvement is evident.
into the staging system. Al-Mefty and Borba\textsuperscript{17} proposed a surgical staging system based on tumor extent and the surgical procedures that would be necessary to achieve a radical resection. The drawbacks of this classification are that they may vary with the surgeon, and a significant number of patients have lesions that are not amenable to radical resection.

RESULTS

The dominant failure pattern after treatment is local recurrence. The chance of salvage after recurrence is remote. Therefore, the probability of local control approximates the likelihood of cure. Because of the indolent natural history, recurrence may be observed many years after treatment, and patients may live with slowly progressing tumor for quite some time. McMaster et al\textsuperscript{1} reported the relative survival rates for 400 patients with chordoma included in the SEER database. Relative survival was defined as the ratio of observed survival for the group to the expected survival based on age, sex, and race comparable mortality for the general population. The relative survival rates for the overall group and the subset of patients with cranial chordomas were as follows: 5 years, 68\% and 65\%; 10 years, 40\% and 47\%; 15 years, 39\% and 48\%. The relative survival rates continued to decline after 15 years, indicating that patients continued to die secondary to disease and/or treatment-related morbidity. Therefore, local control and survival rates should be calculated by actuarial methods and outcomes reported 5 or more years after treatment.

Disease Control and Survival after Surgery. Al-Mefty and Borba\textsuperscript{17} reported on 25 patients with skull base chordomas seen between 1990 and 1996; seven patients had previously undergone surgery, and two patients had received prior radiotherapy (RT). Twenty-three patients underwent 29 skull base procedures. Gross total resection was achieved in 10 patients (43\%), subtotal resection of more than 90\% of gross tumor in 11 patients (48\%), and partial resection of less than 90\% of gross tumor in two patients (9\%). Seventeen patients received adjuvant postoperative proton/photon RT, and two patients received conventional photon postoperative RT. The dose ranged from 60 to 72 cobalt gray equivalent (CGE), with a mean dose of 68.8 CGE. Twenty-one patients had follow-up for more than 3 months (mean follow-up, 25.4 months). Fifteen patients (71\%) were disease free, one patient (5\%) died from intercurrent disease, two patients (10\%) died with disease, and three patients (14\%) were alive with disease.

Gay et al\textsuperscript{18} reported on 60 patients with skull base chordoma (46 patients) and chondrosarcoma (14 patients), who underwent surgery at the University of Pittsburgh between 1984 and 1993. Thirty (50\%) of 60 patients had been previously treated. The extent of resection was as follows: gross total resection, 47\%; near total resection, 20\%; subtotal (≥90\%) resection, 23\%; and partial (<90\%) resection, 10\%. Twelve patients (20\%) received postoperative RT. Patients had follow-up from 1 to 11 years (median, 3.9 years). Five of 46 patients with chordomas died from tumor; the 5-year recurrence-free survival rate was 65\%.

Maira et al\textsuperscript{19} reported on 12 patients with clivus chordomas who were treated surgically at the Catholic University School of Medicine (Rome, Italy) and had follow-up from 14 to 86 months (mean, 40 months). Two of the 12 patients received postoperative RT. Eight patients underwent a gross total resection, and all remained disease-free after a mean follow-up of 38 months. Local recurrence developed in two of four patients who underwent a subtotal or partial resection.

Thieblemont et al\textsuperscript{20} reported on eight patients operated on for skull base chordomas; two of eight underwent an apparent complete resection, and four of eight received postoperative RT. Four patients were alive with disease at 40 to 59 months, two patients died with tumor at 13 and 53 months, one patient was alive and disease free at 2 months, and one patient was alive (status unknown) at 130 months.

Interpreting the surgical data is difficult because of small patient numbers, variable treatment strategies, prior treatment, and short follow-up (particularly considering the long natural history of the disease). Four (16\%) of 25 patients reported by Al-Mefty and Borba\textsuperscript{17} had follow-up less than 3 months, and the mean follow-up was only 25.4 months. In general, gross total resection is possible in less than half of those who undergo surgery. Even in those who undergo a gross total resection, the likelihood of microscopic residual disease is high. The probability of recurrence-free survival after gross total resection is relatively good with short-term follow-up; this is probably due, at least in part, to selection bias. Postoperative RT should be considered for most, if not all, patients.
Disease Control after Subtotal Resection or Biopsy and Definitive Radiotherapy. Fuller and Bloom\textsuperscript{21} reported on 13 patients with skull base chordomas treated with conventional RT after subtotal resection or biopsy at the Royal Marsden Hospital (London) between 1952 and 1981 and had follow-up for 5 or more years. The dose ranged from 45 to 65 Gy (median, 55 Gy) delivered at 1.5 to 1.7 Gy per fraction. Nine of 13 patients died with locally recurrent tumor from 2 to 85 months, one patient was alive with a local recurrence at 49 months, two patients were alive and disease free at 10 and 144 months, and one patient was lost to follow-up. Subtotal resection before RT did not favorably influence survival.

Romero et al\textsuperscript{22} reported eight patients with clivus chordomas treated with conventional RT for gross tumor at the Puerta de Hierro Hospital (Madrid, Spain) between 1975 and 1990, with a follow-up of at least 1 year. Four patients died with tumor at 33, 41, 42, and 52 months, respectively. Three patients had only local recurrence, and one patient had a local recurrence and distant metastasis. One patient died because of intercurrent disease at 103 months, and three patients were alive and disease free at 12, 49, and 103 months, respectively.

Catton et al\textsuperscript{23} reported on 13 patients with clivus chordomas treated with relatively low-dose (median, 50 Gy in 25 fractions over 5 weeks) conventional RT at the Princess Margaret Hospital (Toronto). Twelve patients had tumors that either did not respond to RT or responded and then progressed from 24 to 108 months after treatment. One of 13 patients remained disease free at 93 months.

Terahara et al\textsuperscript{24} reported on 132 patients with skull base chordomas treated with proton/photon RT at the Harvard Cyclotron Laboratory (Cambridge, MA) between 1978 and 1993, with follow-up from 5 to 174 months (median, 41 months). The dose ranged from 66.6 to 79.2 CGE. The median dose was 68.9 CGE. The dose was limited to 60 CGE for the optic nerves and chiasm, 64 CGE for the brain stem surface, and 53 CGE for the brain stem center. The local control rates at 5 and 10 years were 59% and 44%, respectively. Local control was influenced by sex (men had better local control rates than women), minimum tumor dose, and dose inhomogeneity. O’Connell et al\textsuperscript{25} reported on a subset of 62 patients with skull base chordomas treated at the Harvard Cyclotron Laboratory and analyzed the following parameters: sex, age, tumor volume, chondroid appearance, mitotic count, necrosis in the pretreatment biopsy, nucleoli identified at 10× scanning magnification, nuclear pleomorphism, and vascular invasion. Multivariate analysis of survival revealed that women ($p = .001$), tumor necrosis in the pretreatment biopsy ($p = .005$), and tumor volume greater than 70 cm$^3$ ($p = .009$) adversely affected this endpoint.

Noël et al\textsuperscript{2} reported on 47 patients with skull base and cervical spine chordomas treated with proton/photon RT at the Centre de Protonthérapie d’Orsay (France) between 1995 and 2000. The median dose was 67 CGE delivered at 1.8 to 2.0 CGE per fraction. All patients had gross tumor ranging from 1.5 to 10 cm in maximum diameter (median, 4.4 cm), and patients had follow-up from 4 to 71 months (median, 29 months). The 3-year local control and survival rates were 71% and 88%, respectively.

Berson et al\textsuperscript{26} reported on 32 patients with skull base and cervical spine chordomas who were treated with charged particles alone or combined with photon RT at the University of California Lawrence Berkeley Laboratory between 1977 and 1986. All patients had gross disease at the time of treatment. Twenty-five patients had classic chordomas, and seven patients had chondroid chordomas. The 5-year local control rates were 55% for patients with classic chordomas and 36% for patients with chondroid chordomas. In contrast, the 5-year survival rates were 50% for patients with classic chordomas and 80% for patients with chondroid chordomas.

The data after conventional RT are limited; most of the RT data are from facilities where patients were treated with protons or charged particles. The largest series with the longest follow-up is from the Massachusetts General Hospital. Although approximately half of the patients are cured at 5 to 10 years after treatment, it is likely that the cure rate will decline with longer follow-up.

Complications after Surgery. Ten (43%) of 23 patients reported on by Al-Mefty and Borba\textsuperscript{17} underwent a gross total resection. One patient died postoperatively, and two patients experienced a permanent neurologic deficit, including a visual field defect (one patient) and a third cranial nerve palsy (one patient). Transient complications included cerebrospinal fluid leak with meningitis and seventh nerve palsy (one patient), meningitis (one patient), oronasal fistula (three patients),
epistaxis necessitating surgical intervention (one patient), fifth nerve paresis (four patients), and sixth nerve paresis (one patient). Forty-seven percent of 60 patients reported on by Gay et al.18 had gross total resection of the tumor. Three patients (5%) died within 3 months of the surgical procedure. Additional complications included new cranial nerve deficits in 48 patients (80%), cerebrospinal fluid leak in 18 patients (30%), meningitis in six patients (10%), and brain infarcts in two patients (3%). Most new cranial nerve deficits resolved or improved. Forty percent of patients had permanent deterioration of neurologic function after surgery, and 20% had improvement.

Complications after Radiotherapy. Catton et al.23 reported on 13 patients with clivus chordomas treated with moderate-dose conventional RT; no severe complications were observed. Noël et al.2 observed the following complications in a series of 65 patients with chordomas and chondrosarcomas of the skull base and cervical spine treated with proton/photon RT: hypopituitarism, 16 patients (25%); memory impairment, one patient (2%); oculomotor impairment, two patients (3%); severe hearing loss, one patient (2%); and bilateral visual loss, one patient (2%).

CONCLUSIONS
Skull base chordoma is a locally aggressive malignancy that often exhibits an indolent natural history and is difficult to eradicate. Defining the optimal treatment is difficult, because it is a relatively rare tumor that grows slowly and many reports contain small numbers of patients with relatively short follow-up. Although complete resection is desirable, this is often not feasible without substantial morbidity. Most patients are usually treated with RT, either alone or after incomplete resection. Subtotal resection before RT probably does not improve the likelihood of tumor control and should be performed only in situations in which decompression is necessary. Proton/photon RT offers the advantage of increasing the tumor dose while minimizing RT dose to normal tissues, which should reduce the risk of late complications. It is difficult to demonstrate a reduction in the risk of severe complications after proton/photon RT compared with conventional RT, because few patients in the latter group have been reported, and most have recurrent disease develop and are not at risk long enough for late effects to develop. The probability of tumor control after RT is related to minimum tumor dose and dose inhomogeneity.24 A few data pertain to the efficacy of other modalities, such as radiosurgery27 and chemotherapy,28 and the roles of these modalities remain to be defined.

REFERENCES
of 17 specimens with special reference to anaplastic chordoma showing a diffuse proliferation and nuclear atypia. Hum Pathol 1996;27:381–388.


