Chordomas of the craniocervical junction: follow-up review and prognostic factors

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Object. Chordomas are rare tumors that arise from the remnants of the notochord. Because of their deep location, local infiltrative nature, and involvement of surrounding bone, treatment of chordomas is a challenge. In this study the authors analyze the data and prognostic factors obtained during the follow-up period (range 1–150 months, median 38 months) in 53 patients with craniocervical junction chordomas and 10 patients with chondrosarcomas. Methods. Several surgical approaches were used, and some tumor excisions required staged procedures. Survival was calculated according the Kaplan–Meier method. Statistical analysis was performed using Fisher exact, log rank and Kruskal–Wallis tests. Radical/subtotal resection was achieved in 77.8% of the patients. The mortality rate during the follow-up period was 14.3%. In patients harboring chondrosarcoma better 5-year recurrence-free survival (RFS) rates were demonstrated than in those with chordoma (100% and 50.7%, respectively). Histological patterns (typical or chondroid chordomas) and patient age at onset of symptoms had no effect on the RFS rates. Radical/subtotal resections were associated with better RFS rates than partial resection. Adjuvant proton-beam therapy was shown to increase the RFS rates compared with conventional radiotherapy (90.9% and 19.4%, respectively, at 4 years posttreatment). Karyotypically abnormal tumors were associated with the worst RFS rates compared with karyotypically normal lesions (44.5% and 90.3%, respectively, at 3 years). Cases of cranial nerve palsy followed by those with cerebrospinal fluid leakages were the most frequent postoperative complications. Permanent postoperative neurological deficit was observed in 28.6% of the patients.

Conclusions. A better prognosis was observed in patients with chondrosarcoma compared with those harboring chordoma. Histological pattern and patient age at symptom onset were not factors that influenced prognosis in cases of chordoma. Extensive resection and possibly adjuvant proton-beam therapy provided better prognoses for these patients.

Key Words • chordoma • tumor excision • radiation therapy • prognosis • surgical approach

Chordomas and chondrosarcomas are unusual, slow-growing neoplasms. Chordomas presumably originate from remnants of the primitive notochord and are predominantly located in the sacrococcygeal region and in the clivus.23,29,30 Chondrosarcomas are thought to originate from primitive mesenchymal cells or from the embryonal rest of the cartilaginous matrix of the cranium.8,23 Cranial base chordomas usually appear as encapsulated tumors in soft tissues, but they infiltrate bone along the lines of least resistance.23,30 Despite improvements in surgical techniques and our ability to diagnose these lesions, treatment of patients with skull base chordomas and chondrosarcomas is still a challenge for neurosurgeons. Because the tumor originates from the bone at the base of the skull, the recurrence rate of these lesions, even after exceptionally complete resection, remains high.31 Several factors, such as patient age at onset of symptoms, the pathological patterns of the tumor, history of surgery or radiotherapy, extent of resection, adjuvant radiotherapy, and cytogenetic abnormalities, are thought to influence the prognosis of patients with chordomas. The objective of this study was to analyze the follow-up results of a group of patients with chordomas and chondrosarcomas of the craniocervical junction and to determine the prognostic factors for these patients.

Clinical Material and Methods

Patient Population

In this study the authors analyzed data obtained in 63 consecutive patients with chordomas and chondrosarcomas of the craniocervical junction treated by the same surgeon (O.A.) at three different institutions (University of Mississippi Medical Center, Loyola University Medical Center, and University of Arkansas for Medical Sciences) between September 1990 and May 2000. Fifty-three patients harbored chordomas (41 typical and 12 chondroid) and 10 harbored chondrosarcomas. Treatment and results for 25 of
these patients were previously reported\(^1\). In this article we focus on the entire group and analyze recurrence and regrowth rates as well as the prognostic factors for these patients. Fifteen patients with chordomas had previously undergone surgical treatment at another institution. Conventional external-beam radiotherapy therapy was previously performed in five patients with chordomas and in one patient with a chondrosarcoma. There was a female predominance among patients with both tumors (average female/male ratio of 1.21:1 for those with chordomas; 1.5:1 for those with chondrosarcomas). The mean age of these patients was 40.7 ± 15.5 years (range 8–73 years). The clinical manifestations presented at the onset of the disease are summarized in Table 1. The most common signs and symptoms were neuroophthalmological (decrease in vision, blurred vision, and oculomotor nerve palsies), which were observed in 39 patients (61.9%), and headache, which was observed in 11 patients (17.5%). In 25 patients (39.7%), sixth cranial nerve palsy was the most frequent clinical sign. Complete medical, neurological, neuroophthalmological, and radiological evaluations were performed during the pre- and postoperative periods. All patients underwent \(T_1\) - and \(T_2\)-weighted and gadolinium-enhanced MR imaging and bone window computerized tomography studies to determine bone involvement (Table 2). Preoperative and immediate postoperative neuroradiological examinations were performed in our hospitals. Fifty-seven patients (90.5%) attended follow-up sessions for at least 1 month at our institutions after discharge from the hospital. The patients were examined at intervals of approximately 6 months. Forty-one patients (65.1%) were followed in our hospitals and 22 (34.9%) were examined by physicians not affiliated with our respective institutions (with results reported to us). In 30 patients (47.6%), follow-up studies were performed in our hospitals and, in the remaining patients, the studies were performed at several different institutions; in the latter patients neuroimaging studies were forwarded to us and were analyzed by the surgeon and by neuroradiologists in our hospitals.

**Management of Disease**

**Surgical Treatment.** Fifteen patients with chordomas had undergone 41 previous operations and one with a chondrosarcoma had undergone two previous operations elsewhere. Ninety-five surgical procedures (83 in 53 patients with chordomas and 12 in 10 patients with chondrosarcomas) were performed at our institutions. First procedures undertaken in the 63 patients were performed via the following approaches: craniotomy or osteomyectomy/extended craniotomy (26 cases), unilateral/bilateral max-
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illotomy (12 cases), transsphenoidal/extended transsphenoidal (10 cases), transcondylar (four cases), transoral (three cases), anterior cervical decompression and fusion (three cases), suboccipital craniotomy (two cases), retro-
mastoid–petrosal (two cases), and frontotemporal cranioto-
my (one case). Combining the number of previous surger-
ies and the number of those performed at our institutions there were 136 procedures (2.3/patient): 29 patients un-
derwent one procedure, 17 underwent two procedures, six
underwent three procedures, and 11 underwent four or
more procedures. The surgical procedure included removal
of soft tumor tissue and extensive drilling of bone in all pa-
ients. Figure 1 shows an illustrative case of a large chordo-
ma with its epicenter in the clivus and extensions into the
posterior fossa and to the posterior retropharyngeal soft
tissue. The extent of surgical removal was evaluated on the
basis of postoperative MR images obtained during the im-
mediate postoperative period (≤48 hours after the opera-
tion) and 6 months later. The extent of resection was deter-
mined by a neuroradiologist and was classified as follows:
radical (absence of residual tumor or presence of a small
questionable area); subtotal (>90% resection), and partial
(<90 resection). A two-stage operation was indicated in
patients whose tumors extended into anatomical areas pre-
operatively deemed inaccessible via a single approach; a
two-stage procedure was also indicated depending on the
size of residual tumor after the first operation. When we
could not obtain data on the first operation performed else-
where, we considered the operation undertaken at our insti-
tutions to be the “first.”

Radiation Therapy. Radiotherapy was performed in 36
patients with chordomas (12 underwent proton-beam ther-
apy; 13, proton–photon therapy; and 10, conventional ra-
diation therapy) and in one patient with chondrosarcoma
(proton-beam therapy). Conventional radiotherapy was in-
dicated for the first patients in the series and proton-beam
therapy was indicated for the most recent patients, after
data on proton-beam therapy become available in the liter-
ature. In most cases radiation therapy was conducted out-
side our institutions, and data on doses of proton radiation
were available in 12 patients (mean 70.53 CGy, median
72 CGy, SD 5.235 CGy, and range 60–77.4 CGy); da-
data on doses of conventional radiation were available in
only three patients (mean 51.77 Gy, median 55 Gy, SD 5.862
Gy, and range 45–55.3 Gy). Surgery alone was performed
in 18 patients with chordomas and in nine patients with
chondrosarcomas at our institutions, although five among
the former group and one among the latter group had pre-
viously undergone conventional radiation therapy.

Functional Outcome. To assess preoperative, immediate
postoperative (≤48 hours after surgery), and follow-up func-
tional outcome, the KPS was used to measure the de-
gree of disability. Patients were classified into one of three
groups: 1) normal function or minimal symptoms and the
ability to work (KPS score 80–100); 2) independent but not
able to work (KPS score >50 to 70); and 3) moderate or
severe disability (KPS score ≤50). For patients who ex-
perienced tumor recurrence and consequent clinical deteri-
oration, the best KPS score obtained during the follow-up
period was used. For patients who died during the imme-
diate postoperative period, the KPS score acquired before
death was used to indicate both the immediate postopera-
tive period and follow-up scores. Nine patients did not at-
tend 6 months of follow up and did not receive KPS scores
at this time (five patients with typical chordomas, one with
a chondroid chordoma, and three with chondrosarcomas).
Follow-up analysis was performed using the Kaplan–Meier
method to determine overall survival and RFS rates.

Histopathological Diagnosis

Diagnosis of chordomas and chondrosarcomas was
made using the morphological criteria described by Heffelfi-
ger, et al.21 In some cases in which the diagnosis could
not be convincingly established based on morphological
criteria, immunohistochemical studies were conducted.
The pathological findings were compatible with typical
chordomas in 41 patients, chondroid chordomas in 12 and
chondrosarcomas in 10. Only one lesion in a patient with
typical chordoma was considered to exhibit aggressive behavior with some atypical characteristics.

Additional Studies

Cytogenetic Analysis. Flow cytometric DNA analysis was performed in seven patients with chordomas. Karyotype analysis was performed in 18 patients (10 with typical chordomas, four with chondroid chordomas, and four with chondrosarcomas).

Assays for estrogen and progesterone receptors were performed in 13 patients with chordomas. Testing for PCNA was performed in 12 patients with chordomas and in one with chondrosarcoma.

Statistical Analysis

Statistical analysis was performed using the Fisher exact test for comparing proportions and log rank test, and Kruskal–Wallis nonparametric ANOVA (with the Dunn multiple comparisons posttest) for comparison of survival curves and rates. An α error probability not exceeding 5% was considered significant for two-tailed probability tests. The tests were performed using GraphPad PRISM (version 2.0; GraphPad Software Inc., San Diego, CA).

Results

Surgical Treatment

Radical, subtotal, and partial resections were achieved in 31 (49.2%), 18 (28.6%), and 14 (22.2%) of all treated patients. In no patient undergoing partial resection was only a biopsy sample obtained. Twenty-four (45.3%), 15 (28.3%), and 14 (26.4%) of the patients with chordomas underwent radical, subtotal, and partial removal of their tumors, respectively, and radical and subtotal resection was achieved in seven and three patients with chondrosarcomas, respectively. Nineteen patients with chordomas had undergone previous surgery before being treated at our institutions. For those patients with and without a history of surgery, radical resection was achieved in six and 15 patients (31.6% and 44.1%), subtotal resection in three and 15 (15.8% and 44.1%), and partial resection in 10 and four patients (52.6% and 11.8%), respectively. The differences in proportions between radical (p = 0.0022, df = 1 [Fisher exact test]) and subtotal resections (p = 0.0014, df = 1 [Fisher exact test]) achieved in patients with or without a history of surgery were significant. Surgery-related complications were observed in 38 patients (60.3%). Neurological complications were observed in 37 patients: cranial nerve palsy in 22 cases, CSF leakage in five cases; postoperative hydrocephalus in three cases; meningitis, epidural fluid collection/hematoma, pituitary insufficiency, seizures, and quadriplegia in two cases each, and basal ganglia infarction, pneumocephalus, intracerebral hematoma and transient paresis of the superior trunk of the brachial plexus (probably due to stretch during a transcondylar approach) in one patient each. Eighteen patients (28.6%) sustained additional permanent postoperative neurological deficits (cranial nerve palsy, seizures, and vegetative state) and 14 experienced transient postoperative neurological deficits (cranial nerve palsies and quadriplegia). A summary of the affected cranial nerves is presented in Table 3. Of 107 preoperative cranial nerve palsies, 27 (25.2%) were improved after surgery (100%, 66.7%, 50%, and 35.7% of the patients with facial pain [fifth cranial nerve], and fourth, sixth, and seventh nerve palsies, respectively). Of the 22 patients with postoperative cranial nerve deficits, nine experienced transient deficits of one or two nerves (100%, 60%, 60%, and 36.4% of the third, fifth, sixth, and seventh nerve palsies, respectively) and 13 suffered some persistent deficit of one or more nerve. Other complications observed were oronasal fistulas in two cases and severe epistaxis, dislodgment of a tooth, temporal muscle atrophy, nasal septum perforation, sinus mucosa inflammation, middle ear effusion, fluid collection in a thigh wound, asymptomatic mediastinal hematoma, malocclusion of the jaw, pneumonia, retropharyngeal fluid collection, nasal discharge, polyp in the soft palate, venous thrombosis/thromboembolism, and pneumothorax in one patient each. Nineteen patients (61.3%) in whom radical removal was achieved and 13 patients (72.2%) in whom subtotal removal was achieved sustained one or more surgery-related complications (no significant difference, p = 0.541, df = 1; Fisher exact test). Fifteen patients (48.4%) in whom radical removal was achieved and 12 patients (66.7%) in whom subtotal removal was achieved suffered one or more neurological complications (no significant difference, p = 0.3739, df = 1; Fisher exact test). A comparison of postoperative complications observed in patients who underwent radical or subtotal resection of their tumor is presented in Table 4.

Follow-Up Review

The overall clinical and/or neuroimaging follow-up period ranged from 1 to 150 months (mean 46.1, SD 40.2, and median 38 months): 1 to 150 months (mean 49.9, SD 39.5, and median 40 months) in patients with chordomas and 1 to 125 months (mean 28.3, SD 38.7, median 12 months) in those with chondrosarcomas.

Survival. The 5-year survival estimates were 85.9%, 87.8%, and 100%, respectively, for patients with typical chordomas, chondroid chordomas, and chondrosarcomas. There were no significant differences among the survival curves for the three types of tumor (p = 0.3805, df = 2, 2.0; GraphPad Software Inc., San Diego, CA).

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| TABLE 3 | Evolution of cranial nerve palsy in all 63 patients |
|-----------------|-----------------|---------|---------|---------|---------|
| Cranial Nerve   | Preop Deficit   | Improved | Not Improved | New |
| I               | 1               | 1        | 1        |
| II              | 12              | 1        | 11       | 2      |
| III             | 10              | 10       | 4        |
| IV              | 6               | 3        | 3        | 1      |
| V               | 14              | 2        | 12       | 11     |
| V w/ pain       | 6               | 6        | 2        |
| VI              | 28              | 11       | 17       | 3      |
| VII             | 3               | 2        | 1        | 5      |
| VII w/ pain     | 1               | 1        |
| VIII            | 4               | 4        | 4        |
| IX, X           | 10              | 1        | 9        | 1      |
| XI              | 6               | 6        | 1        |
| XII             | 6               | 6        | 1        |
| total           | 107             | 27       | 81       | 32     |
TABLE 4
Surgery-related complications observed in patients who underwent radical and subtotal resections*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Radical Resection</th>
<th>Subtotal Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chordoma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Cranial nerve deficit</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>CSF leak</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Transient quadriparesis of brachial</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Paresis of superior trunk</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

*Complications included fluid collection in the wound, oronasal fistulas (two each), dislodgement of a tooth, septum perforation, sinus mucous inflammation, nasal discharge, middle ear effusion, polyp in the soft palate, malocclusion of the jaw, venous thrombosis/thromboembolism, asymptomatic mediastinal hematoma, and pneumothorax (one each).

Kruskal–Wallis nonparametric ANOVA test; p = 0.68, for the three groups, log rank test). The Dunn multiple comparisons posttest showed no significant difference between curves for patients with chordomas and chondrosarcomas (p > 0.05) or between those with typical chordomas and chondroid chordomas (p > 0.05).

Recurrence-Free Survival. The graph in Fig. 2 upper shows RFS curves for all patients and for patients with chordomas and patients with chondrosarcomas. The 1-year RFS estimates were 82.5%, 80.1%, and 100%, and the 5-year RFS estimates were 54.4%, 50.7%, and 100%, respectively for patients with all tumors, those with chordomas, and those with chondrosarcomas. There was no significant difference among the RFS curves for these three groups (p = 0.1141, Kruskal–Wallis nonparametric ANOVA test). Posttest analysis (the Dunn multiple comparisons test) showed no significant difference between all tumors and chordomas (p > 0.05), but showed a significant difference between the RFS curves for all tumors and those for chondrosarcomas (p < 0.01) and between the curves for patients with chordomas and for those with chondrosarcomas (p < 0.001). The RFS curves according to the histopathological diagnosis are presented in Fig. 2 lower. The RFS estimates were 83.5%, 70%, and 100% at 1 year, and 52.2%, 50%, and 100% at 5 years, respectively, for patients with typical chordomas, those with chordoid chordomas, and those with chondrosarcomas. There was no significant difference among curves for patients with typical chordomas, chordoid chordomas, and chondrosarcomas (p = 0.1114 for all three groups, Kruskal–Wallis nonparametric ANOVA test). The Dunn multiple comparisons posttest showed no significant difference between curves for patients with typical and chordoid chordomas (p > 0.05), but demonstrated a significant difference between those with typical chordomas and those with chondrosarcomas (p < 0.01), as well as between those with chordoid chordomas and those with chondrosarcomas (p < 0.05). The RFS curve demonstrated in patients with chordomas who underwent previous surgery elsewhere was not significantly worse than that observed in patients not previously surgically treated (p = 0.0671, df = 1; log rank test). The RFS estimates were 86.1% and 74% at 1 year and 67.7% and 32.3% at 5 years, respectively, for patients with chordomas with and without previous surgery. There was no difference between RFS curves for patients with chordomas when sex was analyzed as a prognostic factor (p = 0.424, df = 1; log rank test), nor when age at onset of symptoms was analyzed as a prognostic factor (p = 0.4227 for seven groups, Kruskal–Wallis nonparametric ANOVA test). Figure 3 upper presents the RFS curves for the overall population according to the extent of resection. The RFS estimates were 96%, 88.2%, and 53.9% at 1 year and 63.7%, 79.3%, and 15.4% at 5 years, respectively, for patients who underwent radical, subtotal, and partial resections. A significant difference was demonstrated in survival curves among patients who underwent radical, subtotal, or partial resection (p < 0.0001, three groups, Kruskal–Wallis nonparametric ANOVA test). The Dunn multiple comparisons posttest showed no difference in survival curves for patients who underwent radical and subtotal resections (p > 0.05), but showed a significant difference for patients who underwent radical and partial resections (p < 0.0001) and for those who underwent subtotal and partial resections (p < 0.001). Figure 3 lower depicts the RFS curves for patients with chordomas when the extent of resection was analyzed as a prognostic factor. The RFS estimates were 94.7%, 84.9%, and 53.9% at 1 year and 59.8%, 65.9%, and 23.1% at 5 years, respectively, for patients who underwent radical, subtotal, and partial resections. A significant difference was demonstrated among curves for patients who underwent radical and partial resections (p < 0.0001) and for those who underwent subtotal and partial resections (p < 0.001).
Mortality. Nine patients with chordomas died during the follow-up period (overall mortality of 14.3% and mortality rate of 17% for patients with chordoma). Six patients (31.6%) who had undergone previous surgery elsewhere and three patients (8.8%) in whom no previous surgery was performed died during the follow-up period; this difference was significant (p = 0.048). One patient with chordoma died during the immediate postoperative course (surgery-related mortality rate of 1.6% for all patients and 1.9% for patients with chordomas). Eight other patients died due to progression of the disease at 17, 18, 22, 33, 39, 87, 96, and 131 months, respectively, after the first surgery.

Postoperative Functional Outcome

Preoperative and postoperative functional disabilities as assessed using the KPS are presented in Table 5. Preoperatively, eight patients (12.7%) with typical chordomas, chondroid chordomas, and chondrosarcomas had KPS scores of less than or equal to 70, and, postoperatively, 11 patients (17.5%) had scores of at least 70. Of the patients in whom function worsened postoperatively, three harbored typical chordomas. Assessment at 6 months postoperatively showed that three additional patients with typical chordomas also experienced worsened function (KPS score > 70). There was no significant difference between pre- and postoperative KPS scores (df = 1; Fisher exact test) for all patients (p = 1.0), those with typical chordomas (p = 1.745), those with chondroid chordomas (p = 1.5217), and those with chondrosarcomas (p = 1.418).

Radiation Therapy

The RFS rate estimates for patients with chordomas were 90.9%, 19.4%, 38.5%, and 0% at 4 years, respectively, for those who underwent proton-beam therapy, conventional radiation therapy, no radiation therapy, and previous surgery. The differences were significant (p < 0.001, df = 2, Kruskal–Wallis nonparametric ANOVA test). The Dunn multiple comparisons posttest showed a significant difference between radical and subtotal resection (p < 0.001), as well as between subtotal and partial resections (p < 0.001), but a significant difference between radical and partial resections (p < 0.001), as well as between subtotal and partial resections (p < 0.001).
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Additional Studies and Survival

Cytogenetic Findings. Flow cytometric DNA analysis performed in seven patients with chordomas showed diploid populations of cells (DNA index < 1.09) with low numbers of cells in the S phase (< 10%) in three patients, and aneuploid cell populations (DNA index > 1.09), with low numbers of cells in the S phase (< 10%) in four patients. In three patients (60%) with typical chordomas and in one (50%) with chondroid chordomas, aneuploid populations of cells were demonstrated. There was no difference in recurrence rates between patients with diploid cell populations and those with aneuploid cell populations (p = 1.0, df = 1; Fisher exact test). In 11 patients with typical chordoma, three with chordoid chordoma, and four with chondrosarcoma, analysis of karyotypes demonstrated abnormal findings in nine (64.3%) of 14 patients with chordomas (seven with typical chordomas and two with chordoid chordomas) and in one (25%) with chondrosarcoma. There was no difference in the proportions of abnormal karyotypes between patients with typical and chordroid chordomas (p = 1.0, df = 1; Fisher exact test) and between those with chordomas and chondrosarcomas (p = 0.2745, df = 1; Fisher exact test). Recurrence-free survival curves for the 14 patients with chordomas in whom karyotypes were analyzed are shown in Fig. 5. There were significantly more episodes of tumor recurrence in patients with abnormal karyotypes than in those with normal karyotypes (p = 0.01325, df = 1; Fisher exact test), but there was no significant difference between the RFS curves for patients with normal or abnormal karyotypes (p = 0.1955, df = 1, log rank test).

Assays for estrogen and progesterone receptors performed in 13 patients with chordomas were positive for estrogen receptors in one patient (7.7%) and for progesterone receptors in another patient (7.7%). The PCNA assay performed in 12 patients with chordomas and in one with a chondrosarcoma showed an increased index (> 10%) in five patients (41.7%) with chordomas. There was no difference in the proportions of recurrence or in recurrence rates in patients with PCNA values below or above 10% (p = 1.0, df = 1; Fisher exact test).

Discussion

Factors such as pathological patterns, patient age, previous treatment (surgery or radiation therapy), extent of tumor removal, adjuvant postoperative radiation therapy, and cytogenetic abnormalities have been suggested to be related to the prognosis of patients with skull base chordomas and chondrosarcomas.

Pathological Patterns

Heffelfinger, et al.,23 have defined the variant chordoid of chordomas and found it to follow a more benign clinical course, as also stated by others.6 Using the criteria proposed by Heffelfinger, et al., for diagnosis of chordoma in our cases, we did not find a significant difference between survival and RFS curves for patients with typical chordomas and those with chordoid chordomas: this finding lends support to the idea that the distinction of these subtypes has no practical meaning. Patients with chondrosarcomas have much better prognoses than those with chordomas when treated with surgery or adjuvant proton-beam therapy.20,22,39 Analysis of our data corroborates this statement.

Patient Age

The age of the patient has been suggested to have an important role in the prognosis of skull base chordomas.7,13,31

TABLE 5
Preoperative, postoperative, and follow-up functional status*

<table>
<thead>
<tr>
<th>Functional Status</th>
<th>KPS Score†</th>
<th>Preop</th>
<th>Immediate Postop</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>CC</td>
<td>C</td>
<td>TC</td>
</tr>
<tr>
<td>normal or minimal symptoms &amp; working</td>
<td>80–100</td>
<td>36</td>
<td>11 (91.7)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>independent, not working</td>
<td>70</td>
<td>4</td>
<td>9.8</td>
<td>1 (10)</td>
</tr>
<tr>
<td>moderate or severe disability</td>
<td>50</td>
<td>1</td>
<td>2.4</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

* C = chondrosarcoma; CC = chondroid chordoma; TC = typical chordoma.
† For patients with tumor recurrence, the best KPS score obtained during the follow-up period was used. For those who died during the immediate postoperative period, the KPS score obtained before death was used for both the immediate postoperative and follow-up score. Nine patients did not reach 6 months of follow up, and they did not receive scores at this time (five with typical chordomas, one with chordoid chordoma, and three with chondrosarcomas).

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Chordomas in children behave very aggressively and have high levels of mitotic activity, hypercellularity, and pleomorphism. Nevertheless, the prognosis for patients younger than 40 years of age has been suggested to be significantly better than for the older population; the 5- and 10-year survival rates for the younger population were 75% and 63%, respectively, compared with 50% and 11% for the older population. In a review of the literature on children and adolescents with chordomas, Borba, et al. found that the prognosis is significantly worse for patients younger than 5 years of age; however, age was not shown to be a prognostic factor in the evolution of the disease in our patients, when considering division by age.

**Surgical Treatment**

Treatment of patients with chordomas of the skull base is a challenge for neurosurgeons. Because the tumor originates from the bone at the base of the skull, exceptionally complete resection can be achieved. Microscopic total removal of chordoma frequently is followed by the finding of residual tumor in postoperative computerized tomography and MR images. The recurrence rate, even after radical resection, remains high. The deep localization of chordomas at the middle of the skull base makes surgical access to these tumors difficult, and the patterns of spread of various skull base chordomas preclude the use of a single surgical approach. Approaches to skull base chordomas should be based on the characteristics of growth in each case, and sometimes two or more procedures may be necessary to achieve a radical removal. Extensive excision has an important role in the treatment of skull base chordomas; however, sometimes unacceptable procedure-related morbidity may occur. Currently, many authors consider that most cases of chordoma should be treated by resection. The average survival for patients with untreated chordomas is estimated as being 28 months after the onset of symp-

**Postoperative Functional Outcome.** Preoperative, postoperative, and follow-up assessment of disability, as reflected by KPS scores, in patients with chordomas and chondrosarcomas allows surgeons to detect patients whose conditions have worsened due to surgical treatment or due to tumor regrowth or recurrence. Permanent postoperative functional deterioration and improvement assessed using the KPS, usually in 10 points, was observed, respectively, in 40% and 20% of patients with chordomas and chondrosarcoma, respectively. In our series there was no oscillation in KPS scores after surgery, but 7.5% of patients with chordomas experienced worsened function due tumor removal and none of them improved, and another 5.6% experienced worsened function during the first 6 months postoperatively due to tumor regrowth or recurrence.

**Mortality Rate.** The mortality rate for patients with chordomas varies according to the duration of the follow-up period (14–67% in a range of 1.9–5 years median follow-up period), and the surgery-related mortality rate has been reported as 5%. In our study the postoperative mortality rates were 1.6% for all patients and 1.9% for those with chordomas. The global mortality rate during the follow-up period (median 38 months) was 17%, and patients in whom a previous surgery had been performed were at greater risk of death. No patient with a chondrosarcoma died.

**Survival and Recurrence Rates.** Total or near-total tumor resection rates of craniocervical chordomas and chondrosarcomas range from 62 to 78.5%. The estimated overall survival rates for patients with chordomas are 13 to 51% and 18 to 35% at 5 and 10 years after resection, respectively. The frequency of recurrence of chordomas and chondrosarcomas ranges from 12 to 60% for a median follow-up period of 1.9 to 30 years. Overall 5-year RFS rates for patients in whom total or near-total resections and subtotal or partial resections are achieved range from 55 to 84% and from 36 to 64%, respectively. The estimated...
disease-free survival rates range from 33 to 76% at 5 years and from 24 to 76% at 10 years. In patients with a history of surgery, the survival rate is worse than in those without a history of surgery (RFS rates of 64% and 93% at 5 years, respectively). In our series radical and subtotal resections (>90%) were achieved in 77.8% of all patients. In addition, in patients with chordomas, radical or subtotal resection provided better RFS rates than in those in whom partial resection was attained (p < 0.005, three groups, Kruskal–Wallis nonparametric ANOVA test; p < 0.05 for radical/partial resection; and p < 0.001 for subtotal/partial resection, Dunn multiple comparisons posttest). Although there was no significant difference between radical and subtotal resection, the small number and different size of the samples tend to reduce the power of the test and a larger sample will be necessary for further comparisons. In our series in patients harboring chordomas who had not previously undergone surgery elsewhere, there was a better chance of achieving radical resection and better RFS rates than in those who had previously undergone surgery elsewhere (67.6% and 32.5%, respectively, at 5 years). These data reinforce the contention that the extent of resection is correlated with a lower risk of recurrence and that previous surgery is associated with a greater risk of recurrence.

Complications. Gay, et al., reported new cranial nerve deficits in 80% of the patients in their series, and the majority of these deficits completely or partially resolved during the follow-up period. These authors also observed CSF leakage in 30% of patients with chordomas or chondrosarcomas (10% experienced meningitis), and this complication was also correlated with permanent disability. In another report by Menezes, et al., there were no cases of CSF leakage or new cranial nerve palsies. In our series surgery-related complications were observed in 60.3% and neurological complications, mainly cranial nerve palsies, in 58.7%. Additional permanent and transient postoperative neurological deficits occurred in 28.6% and in 22.2% of patients, respectively. On the other hand, 30% of the preoperative cranial nerve palsies improved after surgery. The best chance of postoperative deficit resolution was associated with sixth cranial nerve palsies, followed by seventh, third, and fifth cranial nerve palsies. Preoperative fourth, fifth (facial pain), and seventh cranial nerve palsies were shown to have the best chance of recovery after surgery. The proportions of patients with surgery-related complications who underwent radical and subtotal resection were not significantly different (p = 0.3739, df = 1; Fisher exact test).

Radiation Therapy

Conventional Radiation Therapy. Although chordomas were considered relatively resistant to conventional radiotherapy, this treatment has been used for treating patients with chordomas postoperatively. Conventional radiotherapy does not appear to increase survival duration, but it has been shown to be associated with longer disease-free survival in patients younger than 40 years of age. Although the optimum dose of conventional radiation therapy that should be administered after surgery is controversial, there is some agreement in the literature that if it is to be used, at least 5000 rads should be administered. Despite the small number of cases in our series, based on RFS curves we did not find a significant difference between patients previously treated and patients not treated with conventional radiotherapy elsewhere (p = 0.8051). Based on the RFS curves patients who underwent conventional radiation therapy after surgery had the same prognosis as those who did not.

Proton-Beam or Proton–Photon-Beam Irradiation. In patients with chordomas treated with stereotactic fractionated photon or proton-beam therapy or combined proton–photon irradiation the 5-year actuarial tumor control rate ranges from 68 to 85%, and local recurrences occur in 15 to 31% of patients with a median time to local treatment failures of 32 to 60 months. Hug, et al., reported that in all patients in whom tumors volumes were smaller than 25 ml the tumor remained controlled with 56% of tumors greater than 25 ml. In our series, proton-beam therapy was associated with significantly less risk of recurrence than conventional radiotherapy (p < 0.05). Complications of proton-beam therapy include visual deficits (4.4%), pituitary insufficiency (13.2%), radiation-related osteoradionecrosis of the temporal bone, and radiation effects on the brainstem. In our series these complications were observed in four patients. Characteristically, clinical and radiological signs of radiation-induced necrosis occurred later. Analysis of our data indicates that proton-beam therapy or combined proton–photon therapy is effective in controlling tumor growth. Unfortunately, in all skull base chordomas, vital structures such as the brainstem and optic nerve are in direct relation with the tumor and these structures are the major factor of limitation to this treatment. The better results obtained using proton-beam therapy compared with conventional radiation therapy in our cases have two possible explanations. First, the radiation doses used in proton-beam therapy were higher than those used in conventional radiation therapy (proton-beam therapy can be more conformal than conventional radiation therapy due to the Bragg peak effect and can deliver higher and safety doses). Second, despite equivalent doses, protons have an improved relative biological effectiveness over photons.

Radiosurgery. The role of radiosurgery in the treatment of patients with skull base chordomas has been scarcely reported in the literature. Analysis of available data in cases in which the gamma knife has been used as an adjunct to surgery suggests that this modality can reduce or control the progression of small-volume tumors (< 30 ml). Nevertheless, more data are necessary to form conclusions about the efficacy of gamma knife surgery in patients with these lesions.

Cytogenetic Analysis. Cytogenetic abnormalities have been described in patients with cranial base tumors and the presence of these abnormalities may be of diagnostic and prognostic value. Nevertheless, the findings observed in patients with chordomas did not correlate with prognosis, and some authors have not found chromosome anomalies in these patients. Despite the small number of patients in whom cytogenetic analyses were performed, the presence of aneuploid cell populations seems not to interfere with prognosis of patients, as reflected by the RFS curves (p = 0.05). In our series, abnormal karyotypes were found in 50% of analyzed cases and they were more frequent in patients with chordomas (64.3%) than in those with chondro-
sarcomas (25%). Despite no difference in survival curves of patients with normal and abnormal karyotypes, the recurrence rate was higher in patients with abnormal karyotypes ($p = 0.0042$, df = 1; Fisher exact test).

**Additional Studies and Survival.** We were unable to find previous reports on the roles that steroid assays and PCNA analyses play in the evaluation of skull base chordomas. Assays for estrogen and progesterone receptors performed in seven patients with chordomas revealed low positivity for both (7.7%). Based on our results, assays for estrogen and progesterone receptors, and an elevated PCNA index (> 10%) do not seem to be important for prognosis of patients with chordomas.

**Conclusions**

Chordomas of the skull base are rare tumors, the histopathological findings of which are many times not directly related to the outcomes of the patients. Because of its rarity, few neurosurgeons become familiar with the surgical treatment of the skull base chordoma and, alternatively, other modalities have been used for this with variable results. The development of the skull base surgery made possible radical removal of chordomas. Nevertheless, because of the high morbidity rate and absence of cure, doubts have arisen regarding the value of surgical procedures for treating patients with chordomas. The treatment of chordomas of the skull base remains controversial. In this study we found that the following prognostic factors influence the RFS rate: histological features (chordomas or chondrosarcomas), previous treatment (surgery and, possibly, conventional radiotherapy), extent of resection, adjuvant proton-beam therapy, and, possibly, the karyotype. Analysis of our data also underscores the opinion that the best management of patients with chordomas of the craniovertebral junction is to perform the most extensive resection possible and to initiate adjuvant proton-beam therapy.

**References**


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