Chordomas: uncommon primary bone tumors—17.5% of all primary bone malignancies of the axial skeleton—presumably arising from persistent rests of the notochord. Immunohistochemically, chordomas and the notochord are both strongly reactive to cytokeratin and epithelial membrane antigen. These locally aggressive malignant tumors prefer the spheno-occipital and sacrococcygeal segments of the axial skeleton. In fact, 25–39% of chordomas arise at the clivus. The overall incidence of chordomas is 0.08–0.5 cases per 100,000 individuals per year. The natural course of the tumor is one of relentless progression leading to severe disability and, ultimately, death.

The treatment of clival chordomas has evolved over the years from simple debulking and fractionated radiation to aggressive surgery via skull base approaches followed by particle radiation. More recently, in revisiting older minimally invasive transsphenoidal and transoral techniques, neurosurgeons have used transnasal surgical techniques along with intraoperative imaging guidance and endoscopy. Crockard et al. have almost entirely used midline transfacial approaches to treat these tumors. Although most reports favor radical excision, others do not attribute a survival advantage to patients undergoing such treatment. For instance, Hoch et al. have reported a survival of 81% at 7 years after...
both partial or radical resection and proton beam therapy. Postoperative proton beam treatment has been suggested to afford better tumor control, but other authors have failed to show a clear-cut benefit from radiation.

Thus, although most recent reports have indicated that radical or complete tumor removal provides the best long-term outlook for survival, there is still controversy regarding which factors influence such a resection, the optimal surgical approaches, the associated complications, and even the survival benefit achieved by such a resection. Tumor biological characteristics that may influence survival—such as the Ki 67 labeling index; chromosomal abnormalities; histological factors such as necrosis, mitosis, cellular atypia, and chondroid differentiation; and the expression of adhesion molecules—have been reported. Surgical removal and radiation treatment as well as the biological behavior of the chordoma in an individual are important considerations for survival.

We performed a detailed retrospective analysis of the clinical course of 71 consecutive chordomas arising from the clivus. The tumors were diagnosed and their diagnoses were confirmed using standard WHO histological criteria. The senior author (C.S.) treated the lesions using modern skull base surgical techniques with the aim of achieving radical tumor excision whenever possible. We found that radical tumor excision (that is, no visible disease) offered the best chance of survival. Such resection was directly influenced by the size and anatomical distribution of the tumor. We also analyzed other clinical factors that influence outcomes.

In a separate paper, we will report the results of studying the expression of adhesion molecules (that is, E- and N-cadherin) in relation to patient survival, recurrence, and metastasis.

Methods

Patient Population

Between 1991 and 2005, the senior author (C.S.) treated 71 patients with diagnosed chordomas at the clivus. Six patients were lost to follow-up, leaving 65 patients for the present analysis. The tumors were treated at 2 different institutions (The Mount Sinai Medical Center and St. Luke’s-Roosevelt Hospital, both in New York). An experienced neuropathologist histologically diagnosed all tumors as chordomas based on WHO criteria. There were 47 typical chordomas, 8 chondroid, and 10 dedifferentiated. Immunohistochemical analysis was useful in differentiating these from chondrosarcomas. This series of cases comprises 45 patients with tumors located at the upper and middle clivus (clival group) and 20 patients with lesions at the CVJ (lower clivus–C1; CVJ group). Data for the analysis were compiled from 1) hospital and office records, 2) imaging studies, 3) direct evaluation during postsurgical office visits, and 4) for those who lived at a distance and were unable to come for a direct evaluation, telephone interviews with the patients, their physician reports, or their imaging studies.

Preoperative Evaluation and Follow-Up

The preoperative evaluation has been described in previously published papers and included a thorough neurological and general clinical examination as well as high-resolution MR images, CT scans, and sometimes an arteriogram. Presenting signs and symptoms were similar to those recorded by other authors. Postoperative MR imaging was routinely performed 3 months after surgery. All patients underwent a 6-month clinical and yearly MR imaging and/or CT scanning follow-up study unless an immediate or intermediate imaging study was deemed necessary.

Surgical Strategy and Approaches

Our surgical strategy was to achieve radical resection of the tumor and surrounding bone in all the patients. Dural involvement of the clival chordoma was not accurately predictable based on preoperative imaging. Most of the tumors were completely extradural, while some invaded the outer layer of the dura mater, extended into the space between the outer and inner layers of the dura, or invaded through both layers of the dura into the intradural space. All involved dura and bone were resected as deemed appropriate at the time of surgery. The aggressiveness of our resection was sometimes modified by a patient’s advanced age, physiological status, or explicit desire to limit the scope of the operation. Procedures were performed in either 1 or 2 stages depending on the size and anatomical distribution of the tumor. Tumor excision was recorded as a radical resection in cases in which intraoperative inspection and MR imaging 3 months after surgery did not reveal residual tumor, or as incomplete resection when even a small amount of tumor was left behind at surgery or detected on postoperative imaging. Most authors have classified their radical resection as “gross-total resection” and then subdivided patients with residual tumor into groups according to the fraction of the original. However, we kept our groups simple: those with and those without visible tumor. Since it is impossible to confirm microscopic residual disease, the term “total removal” has been avoided. In all patients who had incomplete tumor resection, we were able to remove > 50% of the tumor.

Clival chordomas characteristically extend into contiguous anatomical areas at the skull base as they grow. Some of these areas may not be accessible by a single surgical approach and may require the use of several approaches at a single sitting or at different sittings. These areas were defined as the clivus, sphenoid sinus, sellar and parasellar areas, temporal bone, infratemporal fossa, retropharyngeal space, parapharyngeal space, C-1, occipital condyle, and jugular foramen.

The surgical approaches used were broadly classified as 1) anterior midline and 2) lateral approaches: 1) extended subfrontal, transmaxillary, transmandibular, endoscopic endonasal, and transcervical; 2) frontotemporal orbitozygomatic, anterior transpetrosal, preauricular infratemporal, combined supra- and infratemporal, and extensive lateral transcen- dylar. Approach selection was based on the location of the main tumor bulk and its relation to the carotid,
vertebral, and basilar arteries, the cavernous sinus, and the brainstem. Whenever the transcondylar approach was used at the CVJ, there was tumor involvement of the occipital condyle, leading to its removal on the side of the operation. An occipitocervical fusion was required in such cases and was performed in 16 patients. Intraoperatively, CT- or MR imaging–based navigation was used in many instances. Endoscopes were used for intraoperative inspection during or after tumor removal or for purely endoscopic endonasal tumor resection.

### Statistical Analysis

The following statistical methods were used in analyzing the results. Differences in percentages between the 2 tumor locations were tested with the Pearson chi-square test, and differences in the means were analyzed using the Student t-test. Results from all the tests are presented as p values. Kaplan-Meier survivor functions were calculated for the survival time and time to recurrence or regrowth, and the log-rank test was used to test for equality of survivor function. In addition, Cox proportional hazards models were fitted, and the results were presented as HRs. The proportion of operations in which radical resection was or was not achieved was compared between groups by using the Pearson chi-square test, and the change in the odds of achieving radical resection by the fold change in tumor volume was calculated with logistic regression analysis. Geometrical mean ratios of the preoperative tumor volume were calculated with linear regression analysis, as were differences in the number of CNs affected. All analyses were performed with Stata, version 9.2 (Stata Corp.).

### Results

#### Summary of the Patients

Table 1 summarizes some of the characteristics of the 65 patients. Overall, the male/female ratio was 1.8:1. In the clival group there was a predominance of males, whereas in the CVJ group there were more females. The average age of patients at the first operation performed by us was 40.7 years (range 7–78 years). Those with tumors at the CVJ were younger than those in the clival group. Forty-two patients underwent primary surgeries at our institutions, and 23 had undergone primary surgery elsewhere. The median time between the initial operation at another institution and the first operation at ours was 25 months (average 39 months, range 1–163 months). Including the initial operations as well as those for recurrences, we performed 80 surgeries in this group of 65 patients. Some patients required repeat operations after our initial surgery: 9 patients underwent 1 subsequent operation, and 3 patients had 2 subsequent operations. The average and median duration of follow-up from the first surgery performed at our institutions were 66 and 60 months, respectively (range 3–189 months).

#### Status of the Disease and Survival

Twenty-two patients (34%) died due to progression of the tumor or complications from it. Radical resection at any initial operation performed at our institutions was achieved in 38 patients (58%). At our initial operation, 73% (16 patients) of the patients who died had incomplete tumor resection. The tumor histological subtypes in the patients who died were typical chordoma in 11 (23.4%),
chondroid chordoma in 5 (62.5%), and dedifferentiated chordoma in 6 (60%). Among the 43 living patients, 36 had typical, 3 had chondroid, and 4 had dedifferentiated chordomas. Twenty-one patients (32%) are alive and free of tumor, whereas 22 patients (34%) are alive with visible tumor. Figure 1 shows the survival curves of the entire study population from the time of diagnosis. The patient’s sex, age at presentation, or tumor location did not affect overall survival, but there was a significant survival advantage for radical resection at our initial surgery.

Figure 2 shows survival from our initial surgery based on whether radical or incomplete tumor resection was achieved and whether patients underwent their first surgery at our institutions or elsewhere. There was a clear benefit of radical resection both in those whose primary surgery was performed at our institutions and in those whose first surgery was conducted elsewhere (p < 0.001 and p = 0.020, respectively). If radical tumor resection was not achieved, the survival was equally poor regardless of a prior surgery (p = 0.533). But if radical resection was achieved, there was an indication that the survival time was slightly shorter in patients with prior surgery (p = 0.059), which could be expected because the time since the initial diagnosis was longer. Overall, survival after our first operation was less frequent among patients who presented to us after a prior surgery elsewhere (Fig. 3) as compared with survival among our primary surgical cases (p = 0.032).

To have a clearer idea of the factors that influenced survival, we further analyzed the 42 patients whose primary surgery had been performed by us (Fig. 4). Survival was significantly improved by achieving a radical tumor resection: 5-year survival of 90% for radical resection versus 52% for incomplete resection (p = 0.001). The number of involved anatomical areas or the tumor size did not directly influence survival but did affect the degree of tumor resection. Patients whose condition remained stable or who improved in their postoperative performance scores survived longer than those whose scores declined (p = 0.003). To further investigate the relationship between the degree of tumor resection and survival, Cox proportional hazards models were fitted, both with the degree of resection as the only independent variable and with the tumor volume, number of involved anatomical areas, and tumor location included as covariates in the model. The Cox model with the degree of resection resulted in an HR of 0.09 (p = 0.002), and the model that adjusted for the other covariates resulted in an HR of 0.08 (p = 0.003).

Twenty-one patients (32%) in the entire group received no radiation therapy; 16 had undergone radical tumor resection, whereas 5 had incomplete tumor resection. The remaining patients received some form of radiation:

![Graphs showing Kaplan-Meier survival functions in the entire patient population (65 patients). Analysis time is expressed in years since the first diagnosis (first operation).](image-url)
Clival chordomas

15 after a primary operation at another institution, 21 after a primary surgery at our institutions, and 8 after subsequent operations. The types of radiation used were as follows: proton beam, 30 patients; fractionated external beam, 12 patients; Gamma Knife, 1 patient; and LINAC radiosurgery, 1 patient. There was no relation between postoperative radiation therapy and survival (Fig. 4).

Degree of Tumor Resection

Radical resection (no visible tumor) was achieved in 38 (58%) of 65 patients at our first operation (Table 2). Patients who had presented to us after a primary surgery elsewhere harbored larger tumors (65% larger tumors) involving more anatomical areas compared with those without prior surgery. Radical resection was achieved in 11 (48%) of these 23 patients. However, radical tumor resection was achieved in 64% of the patients (27 of 42) who had no prior surgery.

The range of preoperative tumor volumes included some extreme values, which distorted the arithmetic mean; therefore, we calculated a geometrical mean value. The preoperative tumor volume had a predictable association with the degree of resection that could be achieved (Table 3). Radical tumor resection was achieved for tumors less than half the volume (46%) of those that had incomplete resection ($p = 0.006$). Doubling of the tumor volume led to a 43% decrease in the odds of achieving radical resection. Larger tumors tended to involve more anatomical areas at the skull base. For example, tumors that occupied 5–6 anatomical areas were 9 times larger than those that involved 1–2 ($p = 0.001$). Patients who had undergone 2-stage operations had tumors that were 3.25 times larger than those in patients who had a single-stage operation ($p = 0.001$).

Among the 80 operations performed in this series of patients, we were able to achieve radical resection of 32 (71%) of the 45 tumors that had $\leq 3$ involved anatomical areas, whereas radical resection was realized in only 14 (42%) of 33 cases with $> 3$ involved areas ($p = 0.011$).

Surgical Approaches: Anterior Midline Versus Lateral

Selection of the surgical approach was based on the size of the tumor and its anatomical distribution. Lesions that extended into multiple anatomical compartments often required more than one surgical approach. Tumors that intimately involved the internal carotid artery or the cavernous sinus or those that had intradural extension with substantial brainstem or basilar and vertebral artery involvement were initially treated using a lateral skull base approach. The midline anterior approaches allowed better access to the tumor base and for the removal of involved clival bone. Therefore, in many

Fig. 2. Graphs depicting Kaplan-Meier survival functions according to a history of prior surgery or a primary surgery performed by us, relative to the degree of resection. Analysis time is expressed in years since the first operation performed by us.
of the larger tumors for which a combined approach or staged surgery was performed, a lateral and an anterior approach were both used (Table 2). Dural reconstruction and the prevention of postoperative CSF fistulas were difficult via the anterior transfacial approaches. Among the primary operations performed by us, 21 were undertaken via a purely midline anterior approach and radical resection was achieved in 13 (62%). Thirty operations were conducted with a lateral skull base approach, and radical resection was achieved in 17 (57%). In 14 operations the anterior and lateral approaches were combined, and radical resection was achieved in 8 (57%). In light of our selection criteria, neither a midline nor a lateral approach provided statistically significant superiority in the ability to achieve radical tumor resection (p = 0.927).

Recurrence, Regrowth, and Spread of Tumor

Among the 65 patients, 32 (49%) had a recurrence or regrowth of the tumor, and, as mentioned above, some of them died (22 patients). Sixteen of these 32 had undergone radical tumor resection at a primary surgery performed at our institutions. Given that 38 patients (among the 65) had radical tumor resection at our primary operation, 42% of patients demonstrated a recurrence following radical resection, whereas at the end of the follow-up period 59% had tumor regrowth and progression following incomplete resection. The mean time to recurrence after surgery for the entire group was 19.9 months (range 1–67 months). The recurrence in 21 patients (65%) occurred within 2 years of our initial surgery. We performed repeat operations in 14 of 32 patients for recurrent disease: 10 had 1 operation, 3 had 2, and 1 had several.

Factors such as tumor location, patient sex, age at presentation, and radiation therapy had no significant impact on the tumor recurrence or regrowth rate (Fig. 5). Patients who had undergone prior surgery had an 81% recurrence/regrowth rate at 5 years from our initial operation, compared with a statistically significant 36% recurrence rate for those whose primary operation (p = 0.001) was performed by us. Patients who received a radical resection had a 5-year recurrence rate of 38% compared with a 70% rate among those who underwent incomplete resection (p < 0.001). More anatomical areas involved by the tumor at presentation meant a poorer outlook for recurrence-free survival (p = 0.006). Younger patients tended to fare better (p = 0.088). To further investigate the relationship between the degree of resection and tumor recurrence or regrowth rate, Cox proportional hazards models were fitted, both with the degree of resection as the only independent variable and with the tumor volume, number of involved anatomical areas, and tumor location included as covariates in the model. The Cox model with only the degree of resection resulted in an HR of 0.30 (p = 0.001), and the model that adjusted for the other covariates resulted in an HR of 0.36 for the degree of resection (p = 0.006).

Seeding of the tumor occurred locally in 4 patients, while distant metastatic disease developed in 2 patients. Both regional seeding and metastatic disease developed in 3 other patients, and 1 patient had a sacral chordoma 26 months after the resection of a clival chordoma. In this latter case, it is difficult to say whether the sacral growth was concurrent or a metastasis, although the patient has shown no other metastatic sites of disease.

Four patients received various forms of chemotherapy for recurrent disease after they had undergone radiotherapy and reoperations for an aggressive type of chordoma. Only 2 of the patients with metastasis are living: one, 5.5 years after the first operation; and the other, 3 years after the first operation.

Surgical Complications

Cranial Nerve Problems. Cranial nerve impairment is the most common presenting feature of chordomas, and worsening of their function is the most common immediate postoperative complication. Many of the deficits noted immediately after surgery tended to improve. Among the 45 patients with clival tumors, 23 presented with CN VI, 11 with CN III, and 9 with CN V dysfunction.

In the CVJ group of 20 patients, 12 presented with CN XII dysfunction; 5 of the 12 showed improvement on follow-up. Eight patients had difficulty swallowing on presentation, indicating dysfunction of CNs IX and X. Nine of the 20 patients had significant worsening of their swallowing function immediately after our surgery. We usually performed an early gastrostomy in case of postoperative lower CN dysfunction. Seven patients required a temporary tracheostomy and 6 required a temporary gastrostomy. Three patients required a permanent tracheostomy: 2 had very aggressive tumors that rapidly recurred, resulting in their demise; and 1 patient had a tumor that recurred many times. One patient is alive with a gastrostomy 8 years after surgery and radiation treatment.

The degree of resection did not influence the likelihood of postoperative CN impairment (Table 4).
was no significant association between the number of surgeries performed in a patient—single or staged—and postoperative CN deficits. Patients who underwent a primary surgery at our institutions had significantly fewer CN problems compared with those who were surgically treated for recurrent disease \((p = 0.001)\). Anterior approaches, as compared with lateral approaches, led to better postoperative CN function \((p = 0.015)\). Lateral approaches often involve working through spaces between CNs, thus increasing the likelihood of manipulation and functional impairment. As indicated above, however, we believed that a lateral approach was safer and allowed better tumor resection in certain situations.

Other Neurological Problems. There were several other postoperative neurological complications. In the clival group, hydrocephalus developed in 6 patients, requiring a shunt operation. Some of these patients also presented with a CSF leak that needed surgical repair. Hemiparesis or monoparesis due to brainstem-related problems occurred in 4 patients, and cerebral or brainstem infarction occurred in 2. One patient had a large postoperative intracerebral hematoma that required surgical evacuation and left the patient severely disabled. Cognitive disturbance or aphasia occurred in 3 patients but resolved during follow-up. Meningitis developed in 7 patients, and wound infections occurred in 3.

In the CVJ group, hydrocephalus requiring a shunt developed in 3 patients. Hemiparesis or monoparesis occurred in 2 patients but resolved during follow-up. Wound infections developed in 2 patients, requiring regional pedicled soft tissue transfer to cover the defect.

Cerebrospinal Fluid Leaks. Although the tumors are primarily extradural, the dura was violated either by the tumor itself or occasionally by the surgical approach. Proximity to the temporal bone, paranasal sinuses, and nasopharynx allows CSF to find egress to the exterior, creating a fistula; therefore, it was important to reconstruct the skull base primarily with vascularized tissue, free fascia, or a fat graft supported in place. The initial treatment for CSF leakage consisted of the insertion of a lumbar spinal drain, unless the leak was profuse at the outset when the patient was reexamined. Among the patients with clivus tumors were 10 postoperative CSF leaks, whereas 4 patients in the CVJ group had CSF leaks requiring reoperation.

Functional Status. Patients with clival chordomas often showed temporary neurological problems immediately after surgery, but most of them improved on follow-
up in 6 months time. The KPS was used to assess patient function before and after surgery, as utilized by other authors. Overall, the mean preoperative KPS score was 86, whereas the mean postoperative score was 84. Of the 80 operations performed in this study, complete pre- and postoperative KPS scores were available for 77. In 39 patients (51%) the score remained stable, in 14 (18%) it improved, and in 24 (31%) it declined. The score declined by 10 points in 17 of 24 patients because of CN involvement, whereas the score decreased by > 10 points in the remaining 7 patients as a result of invasive tumors. The latter patients ultimately succumbed to the disease.

The patients whose scores worsened after surgery had tumors that were 1.98 times the mean volume of those with scores that remained stable (p = 0.042). The improvement seen in some patients after surgery was due to relief of mass effect or relief of pain. Overall survival was significantly better (p = 0.003) in patients whose KPS scores improved or remained stable as compared with the scores in those who decompensated (Fig. 4).

**Discussion**

Although survival from chordomas is generally considered to be poor, there has been improvement with modern treatments. Advances in surgical techniques as well as the administration of high-dose precision radiation therapy have enabled this improvement. Because these tumors are generally considered to be slow growing, the duration of follow-up is very important in evaluating data from the various reported studies. Some of the reports combined patients with low-grade chordomas—sometimes mistaken for chondroid chordomas—with chordomas. Patients with low-grade chordosarcomas have better long-term survival than those with chordomas. The diagnosis of a chordoma must be confirmed by immunohistochemical demonstration of epithelial markers, such as cytokeratin and epithelial membrane antigen.

**Survival and Recurrence**

Patient age and sex and tumor location along the clivus did not influence survival. Radical tumor removal had a positive impact on survival; however, complete tumor removal is a difficult goal to attain, as many authors of contemporary studies have shown. Modern large series of patients have revealed a 5-year survival > 80% when there is no visible tumor after surgery. Which individual characteristics of the tumor affect the possibility of achieving radical resection are not well defined. Most tumors are large by the time they are discovered. Larger tumors and the involvement of several anatomical areas often require multiple operations and approaches to achieve radical tumor removal. We found a definable relationship between the preoperative tumor volume and the anatomical extent of the tumor in determining lesion resectability and therefore patient survival. The radiation therapy literature suggests that patients with tumor volumes < 20–25 ml that were treated with proton beam therapy had better long-term survival. It is more difficult to achieve radical removal in cases of recurrent tumors. Nonetheless, even in patients with such lesions, there is a positive survival benefit if radical removal can be achieved. To exclude the possibility that the same factors that affected resectability were determinants of improved survival rather than the com-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
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<th>Prior Surgery</th>
<th>p Value*</th>
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<td>No. of patients</td>
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<td>42</td>
<td>23</td>
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<td>Tumor location</td>
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<td>33 (78.6)</td>
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<td>Clival</td>
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<td>9 (21.4)</td>
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<td>CVJ</td>
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<td>15 (35.7)</td>
<td>12 (52.2)</td>
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<td>Degree of resection</td>
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<td>27 (64.3)</td>
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<td>Incomplete</td>
<td>44 (67.7)</td>
<td>28 (66.7)</td>
<td>16 (69.6)</td>
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<td>Radical</td>
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<td>14 (33.3)</td>
<td>7 (30.4)</td>
<td>0.811</td>
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<td>Surgical approach</td>
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<td>17.6 (1–241)</td>
<td>28.9 (4–97)</td>
<td>0.123</td>
</tr>
<tr>
<td>Midline ant</td>
<td>3.2 (1–6)</td>
<td>2.9 (1–6)</td>
<td>4.0 (1–6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Lat</td>
<td>21 (32.3)</td>
<td>16 (38.1)</td>
<td>5 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>30 (46.2)</td>
<td>17 (40.5)</td>
<td>13 (56.5)</td>
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<tr>
<td>Combined</td>
<td>14 (21.5)</td>
<td>9 (21.4)</td>
<td>5 (21.7)</td>
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<td>Mean tumor vol (range)†</td>
<td>17.6 (1–241)</td>
<td>28.9 (4–97)</td>
<td>0.123</td>
<td></td>
</tr>
<tr>
<td>Mean areas involved (range)</td>
<td>3.2 (1–6)</td>
<td>2.9 (1–6)</td>
<td>4.0 (1–6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* The p value is calculated from log-transformed data. Abbreviation: ant = anterior.
† The means are geometric means.
pleteness of surgery, a multiple Cox proportional hazard model was fitted, with tumor location, tumor volume, and the number of involved areas included in the model. We found that the degree of resection was the strongest determinant of survival. Thus, radical tumor removal should be pursued whenever possible.

Selection of the surgical approach is an important factor in achieving radical resection. Chordomas are typically extradural tumors. Since the dura is an important barrier against the tumor, an extradural route should be the primary approach, unless the dura is invaded by tumor. Using an intradural approach as the initial method should be avoided because it creates a path for a recurrent tumor, making it an even more difficult problem. Preoperative MR imaging may not accurately predict dural invasion. Several authors have used predominantly lateral approaches and achieved excellent resection, whereas Crockard et al.6 have almost exclusively used the midline anterior approaches to achieve similar degrees of radical resection. More recently, there have been reports of tumor removal entirely by the endonasal endoscopic techniques.15,22,38 Making judicious use of lateral, midline anterior, and combined approaches—as dictated by the anatomy of the tumor—we did not find comparative superiority in any of these approaches. Any surgical team should be versatile in selecting from the range of approaches to remove the tumor as thoroughly as possible. Since the midline anterior approaches follow along long and narrow corridors, endoscopic techniques with the use of intraoperative imaging guidance and navigation substantially enhance the capabilities of such approaches. The rationale used in the present study in selecting the appropriate surgical approaches was as follows: Midline anterior approaches, such as the endoscopic endonasal, extended subfrontal, and, earlier in the study, the transoral, transmaxillary, or transmandibular, were used for reaching the central extradural parts of the tumor. However, we found that the endonasal endoscopic approach allows access to all areas of the central skull base, and the excellent visualization offered by the endoscope along with intraoperative image guidance is superior and less invasive; therefore we now prefer to use this method instead of the other anterior midline approaches. Tumors that extend into the cavernous sinus or surround the internal carotid artery in the cavernous sinus and temporal bone or tumors that intimately involve the vertebrobasilar arteries and the brainstem were approached via a lateral skull base approach. This approach was used for 2 specific reasons that facilitate radical tumor removal: 1) better control of the vessels, allowing safer dissection and repair if necessary, and 2) better separation of the brainstem-tumor interface and subsequently a more secure repair of the clival dura.

Tumor recurrence after apparently complete removal and regrowth of residual tumor after incomplete removal remain difficult problems with chordomas. Although microscopically confirmed complete tumor resection is impossible with chordomas, even a small amount of a tumor’s grossly visible residue increases the chance of its regrowth. Of course, the larger the residual tumor, the sooner its growth will become apparent.9 Recurrence and regrowth of a chordoma have a significantly negative impact on patient survival.9,13 Tumor recurrence after total and near-total excision ranges from 16 to 45% at 10 years.5,6,16,34,48,49 The rate of tumor regrowth suggests 2 types: 1) most tumors, which grow slowly, and 2) those that recur and grow rapidly.6,49 In the present series, 65% of the patients who experienced a tumor recurrence did so within 2 years of our initial operation. Most reported recurrences have occurred within the first 3 years of initial treatment.6,13 Nevertheless, as the duration of follow-up increases, more patients present with recurrences, emphasizing the need for a lengthy follow-up.

**Functional Outcome and Complications**

Complications associated with the treatment of skull base chordomas have been the main deterrent in pursuing radical resection. There is the general impression that radical tumor resection often leads to an increased rate of complications that could have a negative impact on the functional status of patients. However, these potential

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TABLE 3: Preoperative tumor volumes in operations performed in this study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
<th>Tumor Vol Geometric</th>
<th>p Value</th>
</tr>
</thead>
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<td></td>
<td></td>
<td>Mean (95% CI)</td>
<td>Ratio (95% CI)</td>
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<td>overall no.</td>
<td>77</td>
<td>19.6 (14.7–16.0)</td>
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<tr>
<td>degree of resection</td>
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<td></td>
<td></td>
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<tr>
<td>incomplete</td>
<td>32</td>
<td>30.9 (20.6–46.3)</td>
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<td>radical</td>
<td>45</td>
<td>14.1 (9.7–20.6)</td>
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</tr>
<tr>
<td>areas involved</td>
<td></td>
<td></td>
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<tr>
<td>1–2</td>
<td>24</td>
<td>8.0 (4.8–13.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>19.4 (12.7–29.8)</td>
<td>2.42 (1.27–4.60)</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>25.2 (15.6–40.7)</td>
<td>3.13 (1.67–5.86)</td>
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<tr>
<td>5–6</td>
<td>11</td>
<td>72.9 (40.2–132)</td>
<td>9.08 (4.23–19.5)</td>
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<td>op</td>
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</tr>
<tr>
<td>single</td>
<td>54</td>
<td>13.8 (10.0–19.0)</td>
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</tr>
<tr>
<td>staged</td>
<td>23</td>
<td>44.7 (28.6–69.8)</td>
<td>3.25 (1.84–5.72)</td>
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</table>
complications should be considered in light of the poor prognosis of the tumor itself. Impairment of CN function is the most frequent presentation, as well as the most frequent surgical complication. Surgery on recurrent tumors and the use of lateral approaches were associated with a higher likelihood of postoperative CN problems.

Overall, in the present study, there was a slight decline in patient KPS scores after surgery (preoperative mean 86 vs postoperative mean 84); the KPS score remained stable in 52%, declined in 26%, and improved in 21%. Most of the patients whose scores declined showed a decrease of 10 KPS points due to CN problems. Radical resection did not increase the incidence of CN deficits. Postoperative CSF leakage is a significant problem (21% in our series) that often requires reoperation and also increases the risk of infection. The likelihood of its occurrence can be minimized by the judicious use of CSF drainage (for example, spinal drain or ventricular drain) and careful attention to the reconstruction of the skull base. Tumor resection should not be compromised, however.

Tzortzidis et al. have found an overall improvement in the KPS score after surgery (preoperative mean 80 and postoperative mean 86). Pamir et al. have reported 7 new CN palsies in 26 patients, 5 of whom recovered. Two patients had CSF fistulas, and 3 patients required placement of a ventricular shunt for hydrocephalus. Preoperatively, the patients had a mean KPS score of 86.2, whereas postoperatively it decreased to 82.6. Colli and Al-Mefty have noted in a study of 41 patients that 22 patients suffered CN deficits, 13 of which were permanent. Five patients had CSF leaks. A permanent decline in the KPS score occurred in 40% of patients, while scores improved in 20%. In Gay et al.'s study of 60 patients with chordomas and chondrosarcomas, 48 patients acquired new CN deficits. Eighteen patients had postoperative CSF leaks, and 10 of these patients needed reoperations. Fifty patients had a KPS score of 80–100 preoperatively, whereas 46 of them had the same score postoperatively. Crockard et al. have predominantly used anterior midline approaches and found only 6 new CN deficits in their series of 42 patients, although 15 patients suffered CSF leaks.

More serious complications, such as trauma to the brainstem or ischemic events due to injury to perforating vessels, were the main reasons for more severe functional deterioration. These complications occurred in cases of aggressive tumors and were correlated with poor survival results. Careful selection of the operative approach, meticulous microsurgical techniques, and reconstruction of the skull base are important in minimizing complications while achieving radical tumor removal.

Radiation Therapy

Radiation has played an integral role in the management of chordomas. In a series of 48 patients with cranial and spinal chordomas, Catton et al. demonstrated a 100% failure rate with a median survival of 62 months following radiation doses of 40–60 Gy. Pearlman and Friedman showed that doses < 40 Gy are inadequate and proposed that doses > 70 Gy are needed to control tumor.

We could not identify a statistically significant survival benefit from radiation. Our study was limited in assessing this value because of the small number of patients, selection of cases, and variety of radiation modalities.

Although megavoltage fractionated photon beam radiation as well as stereotactic radiosurgery has been
used for the treatment of these tumors, the largest body of data relates to proton beam therapy. Proton beam irradiation seems to extend the duration of survival in the patient with chordoma, but many of the reports on such cases have also included chondrosarcomas. The benefit appears to be in controlling the disease in patients with residual tumor, but its effect on patients with no identifiable residual tumor is unclear. We and some other surgeons have applied a selection bias in administering radiation to patients with residual tumor after surgery. The volume and distribution of the tumor are critical for dose planning as well as the efficacy of the treatment and reduction of complications to the brainstem and optic apparatus. Fagundes et al. have studied the patterns of disease recurrence following proton beam treatment. They found lymph node metastases in only 1% of cases and distant metastatic progression in only 6%. Surgical pathway seeding occurred in only 5% of cases. Local recurrence is by far the leading reason for treatment failure in chordomas, both with surgery and radiation. Fagundes and colleagues found that the mean time to local failure was 24 months, which is in keeping with our findings in the present series. A smaller tumor volume and an adequate distance from the brainstem and optic apparatus increased the likelihood of treatment success. Crockard et al. have used a technique of inserting a fat graft to push the brainstem away from the tumor bed, to maximize the dosage to the brainstem and simultaneously minimize risk, but these investigators could not confirm the survival and tumor control benefit of radiation.

Thus, surgery is aimed at achieving complete tumor removal, but if this goal is impossible, any residual tumor should be a small volume in a localized area away from the brainstem and optic apparatus for optimal proton dose planning.

### Conclusions

Seventy-one patients with clival chordomas formed the present study population, with 65 patients available for follow-up (mean and median duration of follow-up was 66 and 60 months, respectively). Forty-five patients had tumors in the upper and middle clivus, and 20 patients had tumors in the lower clivus and C-1. Patients presenting with tumors at the CVJ were younger than those with lesions at the higher clival location. Radical resection—that is, no tumor visible on postoperative imaging—was achieved in 58% of patients. There was no difference in survival based on patient sex, age at presentation, or tumor location. Radical resection had a significantly favorable impact on survival. Larger tumors and those that occupied multiple anatomical areas had a significantly lower likelihood of complete tumor resection despite multistage operations. Recurrent tumors were associated with a lower chance of radical excision and lower patient survival. The surgical approaches should be planned according to the location, size, and distribution of the tumor, although using a midline anterior approach or lateral approach did not show comparative superiority. Although data supporting proton beam therapy are compelling, the benefit of radiotherapy for the patients in the present series was not clear.

### Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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