Outcome of 132 Operations in 97 Patients With Chordomas of the Craniocervical Junction and Upper Cervical Spine

OBJECTIVE: To study the outcomes of surgery for chordomas of the craniocervical junction and upper cervical spine as well as complication rates, survival, and associated adverse factors.

METHODS: Retrospective review of patients (1982-2007) at 2 European centers who underwent transoral, transfacial, transmandibular, and anterior cervical approaches for excision of chordomas of the craniocervical junction and cervical spine. The χ² test and Fisher exact test were used to determine significant adverse factors (P < .05), and log-rank survival analysis was used to compare outcome in different groups.

RESULTS: One hundred thirty-two operations were performed in 97 patients. The most common operations were transoral surgeries and maxillotomies. After surgery, neck pain was the same or better in 98.1% of patients. Of the 18.6% of patients who presented with myelopathy, 27.8% improved, 44.4% remained unchanged, and 27.8% deteriorated. Major complication rates were velopharyngeal incompetence, 3.1%; vertebral artery stroke, 1%; wound infection, 3.1%; dysphagia, 3.1%; failure of fixation, 2.1%; sepsis, 3.1%; meningitis, 3.1%; and cerebrospinal fluid leakage, 6.2%. Five- and 10-year overall survivals were 55% and 36%, respectively. Patients who presented to our units for revision surgery, after prior attempts at resection elsewhere, were associated with a worse survival than patients who underwent de novo surgery.

CONCLUSION: We present, to our knowledge, the largest published series of chordomas at the craniocervical junction. Complication rates for these major operations can be minimized at specialist centers, with careful patient selection and counseling. As complete or as radical an operation as possible should be performed at first presentation; the best chance for the patient is the first chance.

KEY WORDS: Chordoma; Craniovertical; Outcome; Transoral surgery

Chordomas are rare tumors that arise from remnants of the notochord, a temporary longitudinal structure that orchestrates segmentation of the developing embryo and induces formation of the vertebral column. The notochordal tract begins within the developing sphenoid cartilage, exits posteriorly, and proceeds caudally in front of the basiphysial bone, then into the developing alar ligament and odontoid process and on through the vertebral bodies and disks, as far as the coccyx. By week 10, however, the notochord has degenerated, although remnants of it persist in the nucleus pulposus of the cartilaginous discs.

Chordomas arise from persistent rests of notochordal remnants and are largely restricted to the axial skeleton, commonly in the clivus and sacrum, and were probably first described by Virchow in 1857. They account for 1% to 8% of primary malignant bone tumors and 20% of those arising in the spine. The overall incidence in Europeans is 0.5 per million.

Characteristically, chordomas are slowly growing, expansile tumors that infiltrate local bone and adjacent soft tissues, with a high chance of local recurrence or seeding after resection. Chordomas of the craniocervical junction and upper cervical spine are challenging, not only because of their rarity, but also because of their propensity to recur and their difficult location. Because they are often midline tumors, most can be approached by midline transoral and extended transoral techniques (transmaxillary and transmandibular), as well as high anterolateral retropharyngeal and lateral approaches to the upper cervical spine, and subtemporal or lateral petrous approaches for clival tumors. These approaches
can be associated with significant complications and are not commonly performed in many units. We studied the outcomes and complications for these operations, performed at 2 European spinal units that specialize in surgery for these tumors, to obtain an overview of the complication rates and expected survival after surgery for craniocervical chordomas.

**PATIENTS AND METHODS**

A retrospective review of case records was performed at the National Hospital for Neurology and Neurosurgery, London, United Kingdom, and Klinikum Karlsbad-Langensteinbach, Karlsbad, Germany. It included all patients receiving surgery for chordomas involving any combination of the clivus, C1, C2, or C3, between 1982 and 2007. The majority of these patients underwent surgery by a transoral or extended transoral approach (Figure 1). Patients with isolated chordomas of C3 only and tumors of C4 and below were excluded from this study, because their behavior and the required surgical strategy are likely to differ from tumors of the craniocervical junction. When studying these rare tumors, it is important to compare like with like, and resist the temptation to pool together different locations of tumor that are likely to have inherently different outcomes.

Information retrieved included patient age, sex, dates of diagnoses, surgery, death, comorbidities, preoperative and postoperative Ranawat myelopathy scores, type of surgery and fixation, blood loss, operative details, neck pain, complications, and duration of hospital stay. Survival data were obtained from patient notes, hospital records, and telephone contact with the patient’s referring physician, family practitioner, or relatives, or patients themselves.

Chi-square nonparametric analysis was used (significance level of $P < 0.05$) to determine significant associations between patient variables and complications, or the Fisher exact test (when expected values invalidated the use of the $\chi^2$ test), and Kaplan-Meier survival analyses were used to predict survival and look for significant differences between groups by using the log-rank test. SPSS 16.0 software was used for statistical analyses (SPSS Inc, Chicago, IL).

**RESULTS**

One hundred thirty-two operations were performed on 97 patients for excision of chordomas at the craniocervical junction and upper cervical spine. Sixty patients were treated at the National Hospital for Neurology and Neurosurgery, United Kingdom, and 37 patients were treated at the Klinikum Karlsbad-Langensteinbach, Germany. Fifty-eight patients were male, and 39 were female. Figures 2 through 4 show an example of a C2 chordoma treated by transmandibular surgery. Posterior fixation was performed in all cases, commonly using a Ransford loop and wires before 1992 and the introduction of lateral mass screws and plates from 1992 to 1997. From 1990, the Codman Ti-Frame (Codman, Raynham, MA) and titanium Sofwire system (Codman, Raynham, MA) was also used, and the Synthes Cervifix system (Synthes, Welwyn Garden City, UK) was used from 1999. The DePuy Summit system (DePuy Spine, Raynham, MA) has been used from 2003 to the present day.

Age distribution at presentation is shown in Figure 5, with peak incidence in middle age (41-60 years).

The most common operations performed were the standard transoral operation and “open-door” maxillotomies, the latter being associated with greater complications (Table 1). Figure 6 shows the overall numbers of operations per year.

The mean follow-up period was 50.4 months (median, 41 months; range, 3-186 months). Neck pain was a presenting feature in 86% of patients. This pain was the same or better in 98.1% of patients after surgery, mainly because these patients underwent
fixation procedures that effectively cured the pain of instability. Symptoms of myelopathy were present in 18.6% of patients at presentation, and improved in 27.8% of these, remained unchanged in 44.4%, and became worse in 27.8% after surgery. Of all patients whose neurology remained unchanged, 84.9% were of Ranawat grade 1, 3.8% were grade 2, and 11.3% were grade 3.

Overall complication rates are shown in Table 2. Complication rates were higher in patients with recurrent tumor and revision surgeries, compared with first-time operations ($\chi^2$ test, $P = .05$). However, there was no significant difference in overall survival between patients who had complications and those who did not (log-rank test, $P = .21$). There were no surgical deaths in patients undergoing surgery for the first time. In patients who were undergoing revision surgery, there were also no deaths directly related to the surgery, but within 1 month there was 1 death from a myocardial infarction and 1 from pulmonary embolism.

Nasal regurgitation was more common with open-door maxillotomies compared with the standard transoral operation (Fisher exact test, $P = .025$). This is likely because of the loss in posterior pharyngeal tissue bulk after the more extensive resections possible by maxillotomy, compared with the standard transoral operation. The incidence of nasal regurgitation after transoral surgery with division of the soft palate was not significantly different from that of standard transoral surgery (without division of the soft palate). This implies that the scarring of the soft palate is not the most important factor in producing nasal regurgitation, or velopharyngeal incompetence, but rather it is the loss of pharyngeal tissue bulk that does not allow adequate apposition of the soft palate during swallowing.
Dysphagia was more common with mandibulotomy and glossotomy ($\chi^2$ test, $P = .01$), and this finding was independent of tracheostomy or occipitocervical fixation. There was no significant difference in the rate of sepsis when comparing the standard transoral with the more extensive transmaxillary and transmandibular procedures (Fisher exact test, $P = .61$).

Survival data for the whole group are shown in Figure 7. The median survival was 84 months and the mean survival was 99 months from the date of surgery, with 5- and 10-year survivals of 55% and 36%, respectively.

When survival of patients who underwent standard transoral surgery was compared with survival of those who underwent more extensive procedures, the patients who received more extensive operations seemed to have a worse prognosis, although this was not statistically significant (Figure 8; log-rank test, $P = .22$).

It was interesting to find that patients who underwent primary surgery at the centers of our study had a significantly better prognosis than those who had primary surgery elsewhere and were referred to our centers for surgical treatment of the recurrent tumor (Figure 9; log-rank test, $P = .034$).

**DISCUSSION**

**Methodologic Considerations**

Retrospective data analyses are subject to bias, and prospective data collection should be performed wherever possible.4,5
study is likewise subject to the confounding factors created by the potentially different practices of 2 centers, including nonstandardized resection criteria, approaches, and postoperative radiation treatment. That being said, the overall philosophies of the 2 senior authors, Crockard and Harms, are similar, and comprise radical surgery as the primary treatment. Moreover, their preference for anterior midline surgical approaches to the craniocervical junction have created similar management algorithms at the 2 centers. Chordomas are very rare, and to collect sufficient data for meaningful analysis would involve a very large multicenter study over a long period of time. Apart from the difficulties of starting such a prospective study, data collected over several decades may be difficult to interpret because of the possibility of changes in surgical and medical practice that occur during this period. We have therefore performed a retrospective study and, as far as we are aware, present the largest series of these tumors published to date. The use of the Ranawat myelopathy score is limited by the ceiling effect of this categorical score: it is difficult for patients to improve sufficiently to jump into another category, and therefore smaller clinical changes may go unnoticed. However, for a retrospective study, the Ranawat scoring system is easy and accurate to apply, compared with other scales that rely on prospective questionnaires.

**Interpretation of Results**

Our survival analysis shows 2 groups of patients: those with a higher morbidity and mortality, with recurrence and death within 4 years from initial surgery, and those with a more long-term survival and indolent disease. This is in keeping with data of 38 patients who received surgery between 1958 and 1988, published previously by the senior author, which revealed a subgroup of patients who died within 5 years of surgery, and a second group with almost normal life expectancy.\(^{6}\) In this article, Watkins et al\(^{6}\) also found a slight male preponderance and mean age of 44 years. Differences in survival may be explained by altered expression of chordoma genes.

Pallini et al\(^{7}\) studied tumor gene expression in 26 patients and found that there was a greater chance of recurrence in patients with an increased expression of human telomerase reverse transcriptase messenger RNA and mutation of p53 protein. The Ki67 proliferation index, histologic subtype of the tumor, and degree of necrosis are perhaps less reliable predictors of outcome, possibly because of heterogeneous expression throughout the tumor and sampling error,\(^{7,8}\) although there is a correlation between rapid tumor recurrence and a Ki67 greater than 6%, and older age groups.\(^{9}\)

It is clear surgery has a beneficial effect on life expectancy, despite the risks involved: Eriksson et al\(^{13}\) found that the mean survival for 11 untreated patients with chordoma was less than 1 year. Treatment should start with maximal tumor resection at first
presentation, as suggested by our data (Figure 9), in which better survival was seen in patients who underwent radical surgery from the outset, compared with patients who presented to our unit and received surgery for recurrence after suboptimal primary resection. This is in keeping with the opinion of Crockard et al in a previous article: “The best outlook was associated with the greatest extent of tumor removal achieved during the first operation.” Another factor that may contribute to a worse survival in patients who received primary surgery elsewhere includes the possibility that these patients with recurrence have a more aggressive subtype of tumor from the outset. Complete excision in this context is defined as complete macroscopic excision, which is confirmed by postoperative magnetic resonance imaging. Radical excision is defined as greater than 90% excision, and partial excision is defined as less than 90% resection.16 Carpentier et al compared a smaller group of 22 patients who underwent primary surgery in Paris with 14 who were treated for recurrence after primary surgery elsewhere, and likewise found a significant difference in outcome between the 2 groups (log-rank test, \( P = .049 \)), further supporting the role for aggressive primary surgery.

Tzortzidis et al studied a large series of 74 patients with skull base chordomas, but with a different philosophy of surgical approach compared with our series. Most of their patients underwent subtemporal or extended frontotemporal operations, in contrast to our preference for midline ventral approaches. This may partly reflect differences in tumor location and local referral patterns as well as surgeon’s preference, although the overall mortality and complication rates of these approaches are similar when comparing the outcomes of larger series.10-13 Chordomas in the upper clivus are more likely to be associated with cranial nerve deficits and complications compared with the craniofacial junction tumors, which adds to the difficulty of comparing approaches to different regions. It is more important to achieve maximum tumor excision, and this should be performed with an approach that is best determined by the experience of the surgeon.

Operative Complication Rates

Our complication rates are in keeping with other published series. Colli and Al-Mefty achieved complete excision in almost 50% of their patients and greater than 90% resection in 78%, but with a surgical complication rate of 60%, mainly comprising neurologic complications (28.6% permanent, 22.2% transient) and cranial nerve palsies, but also a 7.9% incidence of cerebrospinal fluid (CSF) leakage, 4.8% hydrocephalus, 3.2% meningitis, and 3.2% oronasal fistulae. They found that complication rates did not significantly increase with greater extents of resection, but there was a correlation of better survival with excision of more than 90% of tumor, giving further support to the concept of radical first-time surgery.

Gay et al documented a higher rate of CSF leakage (30%), probably due to a greater proportion of patients who presented with tumor penetrating the dura. They had a mortality rate of 6.7% and also did not find any differences in complication rates between patients receiving complete excision and those receiving partial debulking.15

In other series, Carpentier et al described 3 postoperative deaths, 3 CSF leaks, and 1 case of meningitis in their series of 36 patients; Pallini et al had 17 significant complications in 26 patients, including 3 CSF fistulae; and Harbour et al documented 3 postoperative deaths in 11 patients.

There is an increased risk of cranial nerve palsies in upper clival tumors, and our previous work has shown that as many as 94% of these patients presented with a cranial nerve palsy, and a 14% incidence of new cranial nerve deficits was seen after surgery.6,10 If patients present with cranial nerve palsies, these often persist despite excision of tumor, and therefore the aim of surgery is more to improve survival.

Survival

Our 5- and 10-year survival times were 55% and 36%, respectively, falling within the range of previously published survival times. Although not statistically significant, there was a trend for better survival after simpler operations (Figure 4). Perhaps this is because patients who required simpler operations would probably have presented with less extensive tumors and therefore had a better survival, rather than improved survival being a direct effect of the surgical method itself. Forsyth et al had similar 5- and 10-year overall survivals of 51% and 35% after surgery, with disease-free survivals of 33% and 24%, whereas Carpentier et al found a significant difference between primary surgery cases (80% and 65% survivals) and cases of recurrent tumor (50% and 0%, respectively), as in our series.

Colli and Al-Mefty documented a longer 5-year survival of 85.9%, but their series included chordoid chordomas, which have often been misdiagnosed in the past and may represent chondrosarcomas. The distinction between chordoma and chondrosarcoma is not always confirmed in pathology departments by the strict use of antibody-labeling criteria. We confirm the diagnosis of chordoma by using a panel of antibodies including S100, cytokeratin, epithelial membrane antigen, carcinoembryonic antigen, and vimentin.6 In our series, chondrosarcomas were excluded, because these are associated with a better survival and therefore their inclusion would introduce bias.

The majority of patients in the United Kingdom center received intensity-modulated radiation therapy after maximal surgery (often 90%-95% excision), whereas some patients from Germany received proton beam therapy. However, in our series the variation in tumor size, location, and surgical treatments made direct comparison of adjuvant radiation treatments impossible. Carpentier et al in their series did not find a significant difference in survival of patients with and without proton beam therapy, but interpretation is again made difficult by patient heterogeneity, the correct classification of chordomas, and varying extents of surgery. Hug et al demonstrated some survival advantage to proton beam therapy, but outcome is probably more dependent on the extent of resection and tumor type. Proton beam therapy and the novel approach of endoscopic skull base surgery show potential in the treatment of chordomas. Whether outcomes and survival can be improved by endoscopic surgery remains to be established, although early results show much promise.
CONCLUSION

Chordomas are unique, rare tumors that are found in difficult places. As complete or as radical an operation as possible should be performed at first presentation, and complication rates can be minimized in specialist centers with careful patient selection and counseling. The best chance for the patient is the first chance. While promising techniques in radiation therapy are evolving, radical surgery is still the cornerstone of treatment for tumor excision and stabilization of the cranio- cervical junction. Repeated surgery can often be required for chordomas, and sometimes it can be difficult to know when to stop operating.

Disclosure

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COMMENTS

Without a doubt, chordomas are rare tumors, and, to be honest, they are seen in neurosurgical facilities only occasionally. In this article, the authors share their vast experience gained in 132 surgical procedures performed in 97 patients with chordomas of the cranio-cervical junction, a truly intricate clinical challenge. This study probably presents the largest series ever published. From the data provided, it becomes obvious that secondary surgery, after prior attempts at resection elsewhere, is associated with a worse survival than that of patients who underwent de novo surgery, or, as the authors put it, the best chance for the patient is the first chance. And this best chance consists of tumor resection at first presentation and as maximal as possible.

Of course, these major operations are not free of complications, and the authors present a work that excels in honesty, since they frankly and sincerely present their complications, which were not few. The authors suggest that, to minimize complication rates, these patients should be treated in specialist centers, and one feels more than obliged to assent to this statement. The authors have performed outstanding work, and the article is a pleasure to read.

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This study analyzes a large series of patients with cranio-cervical chordomas who underwent operations in 2 different centers, either by a transoral approach or by an open-door maxillootomy approach. Chordomas of the cranial base occur in specific sites in the clivus. These include the sphenoclival area (including the cavernous sinuses), the petroclival area, and the foramen magnum (cranio-cervical area). In addition, recurrent chordomas often extend intradurally and are sometimes quite extensive. The surgical challenges in each area are quite different. For foramen magnum and upper cervical chordomas, one may take an anterior approach, as espoused by the authors of this article, or a lateral approach, as followed by myself, Chandra Sen, Ossama Al-Mefty, Bernard George, and others. I prefer the extreme lateral transcondylar approach because, in my hands, it allows for a more complete resection with fewer complications. Most patients also need an occipitocervical fusion, which can be done during or after another operation. Many patients in the United States also receive proton beam radiation, which was not consistently used in this reported series.

A major drawback in this series is that the radiographic images of the patients were not always followed. Therefore, we do not have any idea about radiographic recurrence, and one cannot make any statement about "recurrence-free survival." Only clinical recurrences and mortality are reported.

Notwithstanding these critiques, this is a major publication regarding the outcome of cranio-cervical chordomas operated on via the transoral and maxillootomy approaches. It should be noted that significant swelling difficulties may occur after maxillootomy and glossectomy procedures.

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