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CLINICAL STUDY – PATIENT STUDY

Adjuvant radiation therapy and chondroid chordoma subtype are associated with a lower tumor recurrence rate of cranial chordoma

Brian J. Jian · Orin G. Bloch · Isaac Yang · Seunggu J. Han · Derick Aranda · Tarik Tihan · Andrew T. Parsa

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Abstract Cranial chordomas are rare tumors that have been difficult to study given their low prevalence. Individual case series with decades of data collection provide some insight into the pathobiology of this tumor and its responses to treatment. This meta-analysis is an attempt to aggregate the sum experiences and present a comprehensive review of their findings. We performed a comprehensive review of studies published in English language literature and found a total of over 2,000 patients treated for cranial chordoma. Patient information was then extracted from each paper and aggregated into a comprehensive database. The tumor recurrences in these patients were then stratified according to age (<21 vs. >21 years), histological findings (chondroid vs. typical) and treatment (surgery and radiation vs. surgery only). Data was analyzed via Pearson chi-square and *t*-test. A total of 464 non-duplicated patients from 121 articles treated for cranial chordoma met the inclusion criteria. The recurrence rate among all patients was 68% (314 patients) with an average disease-free interval of 45 months (median, 23 months). The mean follow-up time was 39 months (median, 27 months). The patients in younger group, patients with chordoma with chondroid histologic type, and patients who received surgery and adjuvant radiotherapy had significantly lower recurrence rate than their respective counterparts. The results of our systematic analysis provide useful data for practitioners in objectively summarizing the tumor recurrence in patients with cranial chordomas. Our data suggests that younger patients with chondroid type cranial chordoma treated with both surgery and radiation may have improved rates of tumor recurrence in the treatment of these tumors.

Keywords Chordoma · Recurrence · Radiation · Surgery

B. J. Jian · O. G. Bloch · I. Yang · S. J. Han · D. Aranda · A. T. Parsa (✉)
Department of Neurological Surgery, University of California at San Francisco, 505, Parnassus Ave, San Francisco, CA 94143, USA
e-mail: parsaa@neurosurg.ucsf.edu

T. Tihan
Department of Pathology, University of California at San Francisco, 505, Parnassus Ave, San Francisco, CA 94143, USA

Introduction

Chordoma is an extra-axial tumor that is assumed to develop from the remnants of the notochord [1]. This midline neoplasm has been observed intracranially (35%), in the mobile segments of the spine (15%), but has most commonly been reported in the sacrum (50%) [2–5]. Skull based chordomas are almost always associated with the clivus [6–8]. Chordoma typically presents with lower cranial nerve palsies due to direct compression of the surrounding neural structures. Local invasion of the mass results in high morbidity and mortality as a result of direct brainstem compression. Given their anatomical location and local aggressiveness, cranial chordomas remain problematic for neurosurgeons. Currently, the mainstay of therapy is surgical resection combined with high dose radiation therapy. Despite combined therapy, the recurrence rate remains quite high even with gross total resection. A large volume of literature has been published describing factors influencing the prognosis of patients with cranial chordomas. Much of the data regarding outcomes following treatment has been reported by small case series and case reports which lack statistical power to derive significant conclusions about appropriate management of these tumors. Several factors

are thought to be important in the recurrence of chordomas, including extent of resection, adjuvant radiation therapy as well as histologic subtype. In this analysis we compiled a comprehensive systematic analysis of the English language literature to evaluate the factors associated with recurrence in cranial chordomas.

Methodology

Article selection

Articles were identified via a Pub Med search using the key words "cranial chordoma," "clival chordoma," "skull base chordoma," alone and in combination with "recurrence" as Boolean searches. We then searched all the references in these papers.

Inclusion criteria were: (1) All articles had to specifically follow patients for recurrence (2) Articles had to have enough information of presentations, treatment and follow-up for *each* patient in order to be disaggregated.

Pathological assessment

Chordoma and its chondroid subtype are analyzed in this analysis. In reports that present patient data gathered before the advent of chondroid subtype, all references to the term "chordoma" are assumed to be considered the standard subtype designation. In more recent studies where the chondroid designation was used, pathological confirmation was evaluated but was not always observed. In these cases we assumed that the use of the "chondroid" terminology was based upon pathological confirmation. Data regarding the "dedifferentiated" subtype of chordoma were too scarce and sporadically mentioned to extract this data subset reliably.

Data extraction

Our search resulted in over 2,000 patients treated for cranial chordoma. Of this compiled data set, 760 patients had sufficient date to be disaggregated. Of these 760 patients, 464 of them were followed up for recurrence. All these patients were disaggregated and all references for these articles further scrutinized to ensure the non-duplication of patients and the completion of a thorough and comprehensive review of the literature. In those cases where patients had more than one treatment for recurrence only the initial treatment was considered. In cases where histology was confirmed without any specifications we assume the histology was characteristic of typical chordoma. The age recorded for patients with recurrence, was age of first presentation. All cases that did not have any follow-up data (and no mortality noted) were all excluded. Article data sets that were thought to be incomplete, or that were unable to be disaggregated due to averaged data sets were eliminated from our data sets. Data were analyzed as a whole and stratified into 3 subgroups. The first subgroup divided the data according to patient age with a cut-off age of 21 years. A second stratification divided data based on histological features, group one included those chordomas with typical or conventional histology and group two were those patients with chondroid chordomas (chordomas with prominent chondroid features). The final subgroup analysis stratified the data according to treatment: one group comprised of those patients who received surgery alone as their initial treatment and the second group included those patients who received surgery with adjuvant radiation.

Statistical analysis

Pearson Chi-squared test was used for statistical evaluation of the data. A P value of less than 0.05 (5%) was considered to be significant.

Results

Results of the systematic analysis

A total of 121 articles with 464 non-duplicated chordoma patients met the inclusion criteria for this systematic analysis [9–54, 55–94, 95–129]. The recurrence rate among these patients was 68% (314 patients) with an average disease-free interval of 45 months (median, 23 months).

Clinical variables on recurrence

A total of 53 patients were younger than 21 years of age at the initial time of presentation, while 348 patients were older than 21 years. Surprisingly, the recurrence rate was higher for patients who were older than 21 years old of age, when compared to the younger patients [74% vs. 60%, $P = 0.04$ (Fig. 1)]. Hence younger patients indicated an association with a lower rate of recurrence. A total of 429 patients in our analysis had chordomas with typical histology, while 32 patients had a histological confirmation of chondroid chordoma. The recurrence rate was higher for those patients with chordomas of typical histology [77% vs. 38%, $P < 0.0001$ (Fig. 2)]. Patients with the rarer chondroid chordoma histopathology were associated with an improved rate of recurrence.

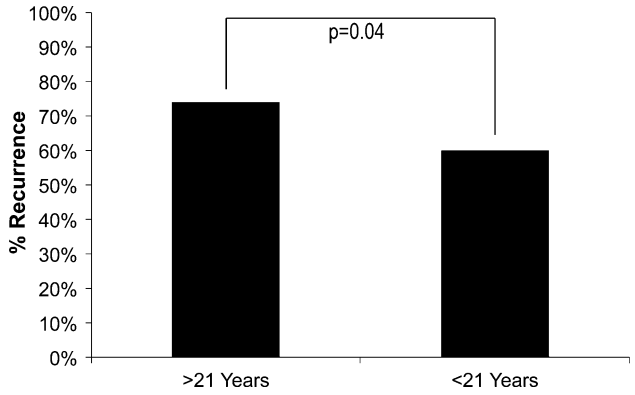

Fig. 1 Recurrence rate by age

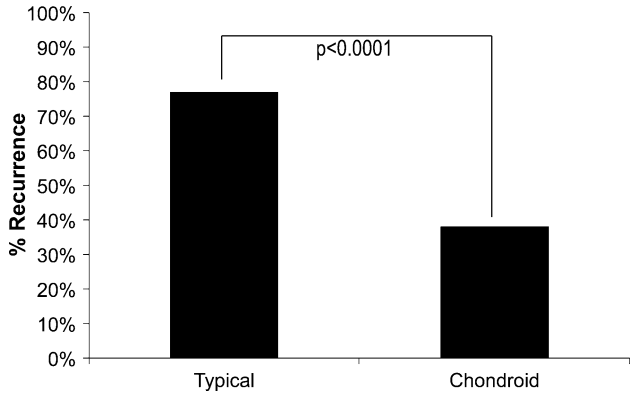

Fig. 2 Recurrence rate by histologic type

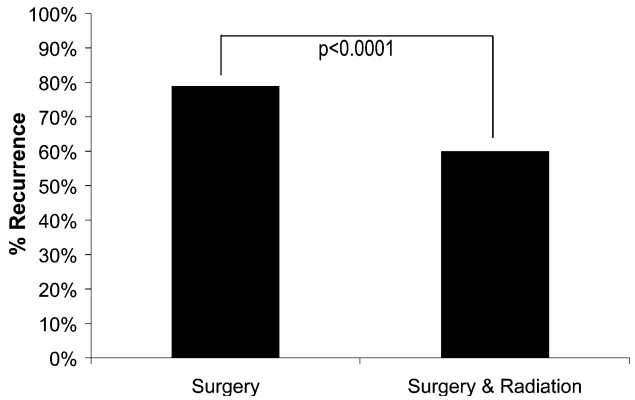

Fig. 3 Recurrence rate by treatment modality

The effect treatment on recurrence

A total of 226 patients had surgery alone, while 128 patients had adjuvant radiation in addition to surgery. The recurrence rate was higher in the group of patients that had surgery alone [79% vs. 60%, $P < 0.0001$ (Fig. 3)]. This statistically significant difference confirms the importance in utilizing a radiation modality in the treatment of cranial chordoma. In our data analysis, more patients were treated with surgery alone despite this lower rate of recurrence associated with adjuvant radiation.

Discussion

Local recurrence is considered by many to be the most significant predictor of mortality in patients suffering from cranial chordomas. In this study we performed a systematic analysis of recurrence in a large population of patients who have undergone treatment for skull base chordomas.

The over-all recurrence rate in our meta-analysis was 68%. This was a little higher than those quoted in the literature by larger studies. For example, one chordoma study of 60 patients with a median follow-up time of 1.9–30 years had a recurrence ranging from 12 to 60% [130]. The average survival time in our study for treated chordoma patients was 3.3 years. This was similar to the survival times reported in the literature after surgery or radiation therapy, or both that ranges from 3.6 to 6.6 years [5, 101, 131]. The disease-free interval in our study, on average was 45 months, with several cases recurring as long as 18 years after the initial treatment [116]. The review of literature reported very similar figures with a 2–3 years time period to recurrence after initial treatment and a few cases of recurrence appearing greater than 10 years after the primary treatment [12].

Chondroid chordomas

The chondroid chordoma subtype diagnosis is a recent addition to the accepted pathological classification system. Given its even more rare incidence, little is known about its pathology in comparison to the standard subtype. One interesting finding in our analysis is that chondroid chordoma was much less likely to recur than chordoma of typical histology. Heffelfinger et al. [132] proposed in 1973, a more benign clinical course for the variant chondroid of the chordoma that he himself had defined. Nonetheless, in 1993 Mitchell et al. [133] refuted the fact that there was a difference in the clinical course between the chondroid and the typical histological variants and attributed this apparent difference to the age of the patient at the time of presentation. Authors stated that it was the high prevalence of chondroid chordoma in younger patients that accounted for the more favorable prognosis and not merely the histology itself. However, our study does not support Mitchell and agrees with the initial observations reported by Heffelfinger. This is demonstrated in the fact that the age range of patients in our analysis with chondroid chordoma ranges from 4 to 72 years and yet still the over-

all recurrence rate in the chondroid patients were lower as a group when compared to the group of patients that presented with the conventional chordoma histology. Our data suggests that the biological behavior for these histological variants is different and the chondroid variant has a more benign clinicopathological course.

Out of a total of 461 patients in our analysis, 429 patients were identified as having typical histology, whereas 32 patients (7.4%) had histological confirmation of the chondroid chordoma subtype. Obviously data gathered from patients prior to the 1980s would not reflect this histopathologic subtype. This prevalence rate observed in this multi-decade meta-analysis is similar to our most recent 10 year institutional experience (unpublished data). At our institution from the years of 1989 to 2008, there were approximately 100 histological confirmed cases of skull base chordomas. In the most recent 10 years (1999–2008) in which the diagnosis of chondroid chordoma was an accepted available diagnosis, there were 5 confirmed cases of chondroid chordomas out of a total of 51 newly diagnosed chordoma tumors (9.8%). In a tertiary institution in which neurosurgical tumors are commonly identified and treated, 1 chondroid chordoma is diagnosed on average every 2 years.

Given the recent acceptance of the chondroid subtype as a distinct pathological variant, it is impossible to cleanly define a prevalence and recurrence rate for this tumor. Data gathered in this meta-analysis covers several decades of case reports and institutional series. The chondroid variant has been an arguably accepted identifiable subtype in the past 1–2 decades. Consequently, it is likely that *typical* chordoma numbers are overestimated in the early years of reporting the occurrence rates. Recent data may be a more accurate assessment of this tumors prevalence and prognostic significance. Only a multi-institutional prospective analysis will be able to address these questions.

It has been suggested that age is a significant prognostic factor in patients suffering from skull base chordomas [20, 134, 135]. Many reporters describe a more aggressive behavior for chordomas in children highlighting the hypercellularity, pleomorphism and high levels of mitotic activity seen in this age group [134]. Moreover, Borda et al. [20] reported that the prognosis is worse in these younger patients because of the extremely diverse and malignant pathological appearance of these tumors observed in children and adolescents. Our analysis does not support these observations and reveals that the recurrence rate was lower in the younger patients younger than 21 years of age. The reason for this observation is unclear but a few authors have previously postulated a worse prognosis for the older population when compared to patients younger than 40 years of age [6]. In our study, both major histological variants (typical and chondroid) as well as the two major treatment modalities (surgery, surgery and radiation) were similarly represented in both groups of patients.

Patients who had surgery and adjuvant radiation treatment had lower recurrence rates than those patients who had surgery alone as several observers have reported increasingly high recurrence rates in surgical patients treated for cranial chordoma, even after radical resection [136]. Although our 60% recurrence rate for patients treated with the combination modality of both surgery and radiation was actually higher than those quoted in the literature of 15–32% [32, 137–142] we strongly believe that cautious resection followed by post-operative proton-beam radiotherapy epitomizes the best therapeutic approach. Proton-beam therapy is thought to be a more effective means of radiation therapy as it gives a more concentrated dose to the tumor bed without much spread to surrounding tissues. The narrow beam of proton-beam therapy allows significant doses to be given to areas of the skull base without toxic doses spreading to nearby brainstem structures. Furthermore, although adjuvant radiation is associated with a lower rate of recurrence for cranial chordoma, most patients in this analytical series were treated with surgery only instead of surgery with radiation. Our data suggests that radiation therapy should be seriously considered as an adjuvant treatment for cranial chordomas.

Conclusion

In conclusion, we report our results from a large disaggregated systematic analysis of the English language literature regarding recurrence among cranial chordoma patients. We hope that by using such a large data set, we are able to summate the aggregated data set and identify recurring characteristics in the pathobiology of this tumor and its response to treatment. Our data confirms that adjuvant radiation is an important factor in a lower rate of recurrence and also suggests that younger patients with a chondroid subtype may have a lower rate of recurrence.

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