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A systematic review of intracranial chondrosarcoma and survival

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Abstract

Most data regarding survival in patients with chondrosarcoma are limited to case studies and small series performed at single institutions. A systematic review was performed to study the relationship between proposed prognostic factors and survival. Every study published in the English literature was reviewed. The mortality rates in these patients were analyzed according to modality of treatment, treatment history, histological subtype, and histological grade. A total of 560 patients with cranial chondrosarcoma were analyzed. Median follow-up time was 60 months. The 5-year mortality among all patients was 11.5% with median survival of 24 months. Mortality at 5 years was significantly greater for patients with tumors of higher grade or of the mesenchymal subtype, or had received surgical resection alone, when compared to their respective counterparts. The results of our systematic review provide useful data in predicting survival among cranial chondrosarcoma patients.

Keywords

Cranial chondrosarcoma; Survival outcomes; Systematic review

1. Introduction

Chondrosarcoma accounts for 6% of skull base neoplasms and 0.15% of all intracranial tumors¹. They are subclassified into the conventional (hyaline/myxoid), dedifferentiated, clear cell, and mesenchymal subtypes². In accordance with the current literature, the conventional type of chondrosarcoma is the most common cartilage tumor to develop in the skull base³. Conventional chondrosarcoma is composed of either hyaline cartilage, myxoid cartilage or a combination of both of these matrices. The hyaline subtype is characterized by hypercellular hyaline cartilage containing cytologically atypical chondrocytes within lacunae. In contrast, the atypical chondrocytes of the myxoid subtype do not reside in lacunae but instead are enmeshed in a flocculent myxoid matrix. The mesenchymal subtype is known to display a more anaplastic appearance.

The significance of histological subtypes among chondrosarcomas has been reported; however, the prognosis is determined primarily by its World Health Organization (WHO) histological grade. The grading system consists of three categories: grade I (well

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differentiated), grade II (moderately differentiated) and grade III (poorly differentiated). Although malignant, the biological behavior of these tumors is characterized by potentially fatal progressive enlargement and subsequent compression or invasion of local structures such as the brain and the optic pathway, hence diplopia and headache, the two most common presenting symptoms recorded in these patients. The complete surgical resection of these tumors is most often prevented by their deep location; consequently, a combination of surgery and irradiation has become the mainstay of treatment⁴⁻⁷. Factors such as pathological pattern, previous treatment (surgery or radiation therapy), degree of tumor resection and adjuvant postoperative radiation therapy have all been implicated in the prognosis of patients with chondrosarcoma.

Although most chondrosarcoma arise *de novo*, they are common in patients with Ollier's disease, Maffucci syndrome, Paget's disease and osteochondroma. One postulated theory for the development of intracranial chondrosarcoma highlights that while the bones of the skull vault develop primarily by intramembranous ossification, the bones of the skull base mature predominantly by endochondral ossification⁸. Endochondral ossification is also responsible for the development of several sites in the mature skull including a large part of the petrous portion of the temporal bone, areas of the petro-occipital, sphenoid-occipital, and sphenoid-petrosal synchondrosis. Intracranial chondrosarcomas might develop from the chondrocytes within rests of endochondral cartilage that may be present in these areas. Others believe that the primitive multifunctional mesenchymal cells involved in the embryogenesis of the skull base and temporal bone may be the source of these tumors. Yet other authors contend that intracranial chondrosarcomas develop from metaplastic mature fibroblasts^{9,10}.

Presently, there is much literature published on intracranial chondrosarcoma emphasizing the effect of histological subtypes, grading and treatment outcomes in these patients. Despite all these efforts, significant interpractitioner variability of practice approaches still persists, given that most of these studies are case studies, small to modest size case series and frequently from single institutions, and thus lack the statistical power and freedom from single surgeon bias to guide the new individual practitioner along the path of best management in the approach to these patients.

Consequently, we report a comprehensive review of the English language literature to assess survival in patients treated for intracranial chondrosarcoma and stress the relationship between the proposed prognostic factors and survival.

2. Methods

2.1. Article selection

Articles were identified via a Pub Med search using the key phrases "cranial chondrosarcoma," "clival chondrosarcoma," "skull base chondrosarcoma," "intracranial chondrosarcoma" alone and in combination with "survival" as Boolean searches. An extensive review of cited references was performed.

Inclusion criteria were that: (i) all patients had to have follow-up data available; and (ii) articles had to have enough information for the data from each patient to be completely disaggregated.

Exclusion criteria were: (i) all articles that combined patient outcomes of chondrosarcoma and chordoma were excluded, unless there was a clear distinction between the two separate groups of patients; (ii) all chondrosarcomas originating from the head and neck were excluded; and (iii) all patients with Ollier's disease, Maffucci syndrome (enchondroma with multiple angiomas), Paget's disease, and osteochondroma were excluded from our analysis.

2.2. Data Extraction

Our search resulted in over 2,000 patients treated for cranial chondrosarcoma. Of these, 630 patients were completely disaggregated. Of these data for 630 patients, 560 received appropriate follow-up. All these studies were completely disaggregated and all references for these articles were further scrutinized to ensure the non-duplication of patients and the completion of a thorough and comprehensive review of the English literature.

Where patients had more than one treatment for recurrence, only the initial treatment was considered. Where the histology was confirmed without any specifications patients were classified as conventional chondrosarcoma. The age recorded for patients with recurrence was the age at first presentation.

Data were analyzed as a whole and stratified into 4 groups. The first analysis divided the data into 2 groups according to patient treatment: patients undergoing surgery only; and patients who received surgery combined with postoperative adjuvant radiation treatment. A second stratification divided data based on treatment history into 2 groups: group 1 comprised patients who had received previous treatment; and group 2, patients who were being treated for the first time. A third analysis divided patients into 2 groups based on histological subtypes: group 1 included those chondrosarcomas with conventional histology; and group 2 represented the mesenchymal subtype. The final analysis stratified the data into 3 groups according to histological grading: grade I; grade II; and grade III with each grade comprising one group.

2.3. Statistical analysis

A Pearson chi-Squared (χ^2) test was used for the statistical evaluation of the data. The p value was considered significant at the 5% (0.05) level.

3. Results

A total of 560 non-duplicated chondrosarcoma patients met the inclusion criteria for this systematic review^{1,11-108}. The overall 5-year mortality rate among all patients was 11.4% (64 patients) with an average survival time of 53.7 months (median, 24 months). Most of the chondrosarcomas in our study involved the clivus (32%), while the second most common location was the temporo-occipital junction (27%). The most common presenting symptom was diplopia (11%), closely followed by headache (9%). Some cases in these articles were eliminated from the analysis for reasons of missing data, obscure data presentation (e.g. studies that presented chondrosarcoma and chordoma patients grouped together), and yet several others had to be excluded because they were not available in the English literature.

3.1. The Effect of Treatment on Survival

A total of 161 patients had surgery alone, while 325 patients had surgery in addition to postoperative adjuvant radiation therapy. Not surprisingly, the 5-year mortality rate was higher in the group of patients that had surgery alone (25% versus [vs.] 9%, $p < 0.0001$) (Fig. 1).

3.2. The Effect of Previous Treatment on Survival

A total of 68 patients received previous treatment, while 492 patients were being treated for the first time. Surprisingly, there was no difference in mortality between these two groups of patients (10% vs. 12%, $p = 0.492$) (Fig. 2).

3.3. The Effect of Histological Subtype on Survival

There were a total of 452 patients in our analysis who possessed chondrosarcomas of the conventional subtype, while 60 patients had the mesenchymal subtype. As expected, the mortality rate was lower among patients with the conventional subtype (6% vs. 54%, $p < 0.0001$) (Fig. 3).

3.4. The Effect of Histological Grade on Survival

A total of 364 patients had grade I, 80 patients had grade II, and 8 patients had grade III chondrosarcoma. Not surprising, the lowest mortality rate was among the patients with grade I (5%), and the highest mortality rate was observed in the grade III group (25%), with the grade II in the middle with a 10% mortality (5% vs. 10%, $p = 0.144$; 10% vs. 25%, $p = 0.143$; 5% vs. 25%, $p < 0.012$) (Fig. 4).

4. Discussion

The prognosis of patients with intracranial chondrosarcoma is strongly influenced by several significant factors. These factors include the use of postoperative adjuvant radiation therapy, pathological pattern, previous treatment (surgery or radiation therapy) and extent of tumor removal. However, local recurrence is considered by many to be the most significant predictor of mortality in these patients. For this reason, the review of literature on this topic reveals a large number of publications put forth by many different observers, but there have been few if any efforts to combine this research to achieve the statistical power needed to determine the appropriate methods to manage these tumors. In this study we performed a meta-analysis of survival in a large population of patients who has undergone treatment for intracranial chondrosarcomas.

The overall 5-year mortality among patients in our study was 11%, with an average survival time of 53.7 months (median, 24 months). This percentage was almost identical to those quoted in the literature. For instance, Oghalai et al.¹⁰⁹ in his study involving 33 patients with skull base chondrosarcomas had an overall mortality of 15%. The high survival rate among these patients was even further emphasized by Colli and Al-Mefty¹¹⁰ and by Oghalai et al.¹⁰⁹ on two separate occasions who revealed 5-year survival rates of 100% and 85%, respectively. For comparison, the survival for chondrosarcoma that is remote from the cranium, such as the spine, is about 41%^{111,112}

Our study found that chondrosarcoma patients treated with surgery alone demonstrated a 5-year mortality rate of 26%, while the implementation of postoperative adjuvant radiation therapy reduced this mortality rate dramatically to 4%. These numbers were not surprising because many recent studies have stated, without reservation, that meticulous surgical resection together with postoperative radiotherapy provides the best long-term outcomes for these patients. One such study by Isaacson et al.¹¹³ in 2007 clearly states that radiation therapy is an important adjunctive therapy in the management of chondrosarcomas; a study by Neff et al.¹¹⁴ in 2002 asserts that postoperative radiation therapy may be beneficial in these patients.

Nonetheless, the epitome of the idea regarding high survival and low mortality in chondrosarcoma patients is a study managed by Rosenberg et al.¹¹⁵ in 1999. This is the largest study, to date, on chondrosarcoma of the skull base in which treatment was carried out at a single institution. This study consists of 200 patients and quotes 5-year and 10-year disease-specific survival rates of both 99%, when surgery is combined with high-dose fractionated proton beam radiation. Although our survival rate (89%) is slightly lower than theirs, this can most likely be attributed to the combination of all the different type of radiation therapy into one large group to maximize the statistical power in our study. In our

study, the history of previous treatment did not prove to be a significant indicator of mortality. This coincides with a study done in 2005, which also did not find any correlation between patients undergoing previous treatments and mortality¹⁰⁹. On the contrary, Tzortzidis et al.¹¹⁶ revealed in 2006, that patients who required multiple operations had a diminished disease-free survival.

The four major subtypes of histological classification are: conventional, mesenchymal, clear cell and dedifferentiated. The review of literature revealed no clear cell or dedifferentiated subtypes occurring intracranially. Consequently, our analysis included only the mesenchymal and conventional subtypes. In our study, those patients possessing chondrosarcomas of the conventional subtype had a 6% 5-year mortality, while those chondrosarcoma demonstrating the mesenchymal subtype carried a much higher mortality rate of 54%. This was expected since the mesenchymal subtype indicated worse clinical behavior and poorer prognosis than conventional histology according to Oikawa et al.¹¹⁷ Furthermore, according to Koch et al. 2000¹¹⁸, labeled mesenchymal histology as well as grade of the tumor were cardinal factors that portends a poor prognosis. This grading system is important because it reflects prognosis based on tumor biology distinct from its location or stage of presentation¹¹⁴. Evans et al.¹¹⁹ reported five-year survival rates of chondrosarcomas grade I, II, and III to be 90%, 81%, and 43%, respectively. Our study demonstrated 5-year survival rates of 95%, 90%, and 75% for grades I, II, and III, respectively. In comparison, chordomas, another intracranial skull base tumor, do not appear to have histology as a significant prognostic factor, but for chordoma, age might be an important variable in survival^{110,120-124}.

Although adjuvant radiation therapy appears to reduce the mortality rate of chondrosarcomas, further investigations into the usefulness of adjuvant therapy for low-grade chondrosarcomas must be performed. It is possible that low-grade chondrosarcomas have good survival prognosis with surgery alone and be better served with resection without immediate radiotherapy or with delayed adjuvant radiation.

The wide heterogeneity of the articles included in our systematic review precluded us from further stratification and analysis. Prospective studies could be designed to further investigate survival after treatment for intracranial chondrosarcoma. Inconsistently assessed and reported variables cannot be analyzed with regression and is problematic with the heterogeneous nature of the reported literature. Aggregated systematic reviews may help to identify important prognostic factors and clinically relevant indicators for survival^{125,126}. There are, although, several inherent limitations with systematic reviews¹²⁷. One clear limitation is that the systematic data is only as good as its composite studies, and may inherently reflect source study biases. However, the large number of patients in our analytic review helps to mitigate the biases and dilutes the inherent error of any particular article.

In conclusion, we report our results from a comprehensive systematic review of the English language literature regarding survival among cranial chondrosarcoma patients. It is our hope that by using such a substantially large data set we are able to minimize the effect of individual surgeons and the bias of any individual institution on the outcome of these patients and thereby create a more objective protocol for clinicians managing these patients.

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Fig. 1.
The effect of treatment on the 5-year mortality rate from chondrosarcoma showing that mortality was higher in patients who had undergone surgery only.

Fig. 2.

The effect of previous treatment on the 5-year mortality rate from chondrosarcoma showing that treatment history had no effect.

Fig. 3.

The effect of histological subtype on the 5-year mortality rate showing that mortality was lower among patients with the conventional chondrosarcoma subtype.

Fig. 4.

The effect of histological grade on the 5-year mortality rate showing that mortality increased with a corresponding increase in World Health Organization grade (I–III) chondrosarcoma.