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Review Paper
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Chondrosarcoma of the jaw bones: a review of 224 cases reported to date and an analysis of prognostic factors

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L. L. de Souza, F. S. C. Pontes, F. P. Fonseca, D. S. da Mata Rezende, V. C. S. Vasconcelos, H. A. R. Pontes: Chondrosarcoma of the jaw bones: a review of 224 cases reported to date and an analysis of prognostic factors. Int. J. Oral Maxillofac. Surg. 2019; 48: 452–460.

Abstract. The objective was to integrate the available published data on chondrosarcoma (CHS) of the jaw bones into a comprehensive analysis of its clinical and histological features, treatment, and prognostic factors. An electronic search was undertaken in October 2017. To be eligible, the publication had to provide sufficient clinical/histological data to confirm the diagnosis. One hundred and ten publications (224 cases of CHS) were identified and included. There was a slightly higher prevalence of CHS in males than in females. Most subjects with CHS were in the second to fifth decades of life. The most common symptom was swelling and the most commonly observed location was the maxilla. Histologically, most tumours were of the conventional type and were low grade tumours. The treatment of choice was tumour resection. Histological grade, treatment with chemotherapy alone, and the presentation of recurrence or metastasis were found to be significant independent prognostic factors: patients who presented high-grade tumours, who received chemotherapy alone as the treatment of choice, and those who presented recurrence or metastasis were more likely to have a worse prognosis. In addition, radical surgery associated with radiotherapy as the treatment protocol showed a better prognosis.

Key words: chondrosarcoma; bone lesion; jaw bones; prognostic.

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Chondrosarcoma (CHS) of the jaw bones was first described by Miles in 1950[1]. This first report described two cases of CHS affecting the maxilla in female patients, one aged 47 years and the other aged 51 years, both of whom died from the disease. CHS is a malignant cartilaginous tumour characterized by the formation of cartilage by tumour cells[2–4]. The lesions present in the form of several different subtypes: conventional, mesenchymal, dedifferentiated, myxoid, juxtacortical, and clear cell[5]. In addition, the tumours can be categorized into three different subtypes (I–III) according to the cell density, nuclear differentiation, and size of the nuclei[5,6].

CHS in the jaw bones is considered a rare lesion. As a result, there is limited information in the literature regarding their clinical and histological features, treatment, and prognostic factors. The epidemiological study of such rare lesions is of great importance as it indicates the diagnostic accuracy and allows pathologists and surgeons to make informed decisions and refine treatment plans to optimize clinical outcomes[7].

The aim of this study was to integrate the available published data on CHS of the jaw bones reported in the literature into an up-to-date comprehensive analysis of their clinical and histological features, treatment, and prognostic factors.

Materials and methods

This study followed the guidelines laid down in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[8].

Search strategies

An electronic search without times restrictions was undertaken in October 2017 in the PubMed (National Library of Medicine, National Institutes of Health), ScienceDirect, and SciELO databases. The following terms were used in the search strategies: (chondrosarcoma and head and neck) and (chondrosarcoma and jaw) and (chondrosarcoma and mandible) and (chondrosarcoma and maxilla) used separately.

The reference lists of the identified studies and relevant reviews on the subject were also scanned for possible additional studies. Publications reporting lesions identified as being CHS, even without the term 'chondrosarcoma' in the title of the article, were also re-evaluated for the present study.

Inclusion and exclusion criteria

To be eligible, the publication had to report cases of CHS and provide sufficient clinical/histological data to confirm the diagnosis. El-Naggar et al. have described the microscopic parameters for CHS[5]: (1) abnormal cartilage showing atypical nuclei and nucleoli, hyperchromasia, and infiltration of lamellar bone; (2) increased cellularity; (3) irregular spacing of chondrocytes. Cases that did not include these parameters were not included in this analysis. With regard to the histopathology of CHS, three different grades of differentiation are described according to the presence of increased cellularity, pleomorphism, multinucleation, and mitoses. The histological grade was determined on the basis of the updated World Health Organization Classification of Head and Neck Tumours published in 2017[5].

In order to have a clear and proper understanding and appropriately identify the microscopic parameters described in the text, articles were included only when published in English, Portuguese, or Spanish. Controlled clinical trials, cohort studies, cross-sectional studies, case–control studies, case series, and case reports were eligible for inclusion.

Immunohistochemical studies, histomorphometric studies, radiological studies, genetic expression studies, histopathological studies, cytological studies, cell proliferation/apoptosis studies, and in vitro studies were excluded, unless any of these publication categories included reported cases with sufficient clinical, histological, and radiological information. In addition, papers that did not report the maxilla or mandible as the primary location, the histological grade, or the treatment were excluded. Furthermore, papers that presented radiation-associated lesions were excluded from the analysis.

Study selection

The titles and abstracts of all articles identified through the electronic searches were read independently by all five review authors. For studies appearing to meet the inclusion criteria, or for which there was insufficient information in the title and abstract to make a clear decision, the full-text report was obtained. Any disagreement between the authors regarding article selection was resolved by discussion. The clinical and radiological aspects, as well as the histological description of the lesions reported in the publications, were assessed thoroughly by three authors who are expert in oral pathology (FSCP, FPF, and HARP), in order to confirm the diagnosis.

Data extraction

Two groups of review authors (LLS, DSMR, and HARP; FSCP and FPF) independently extracted the data using a specially designed data extraction form. Any disagreement in the data extraction was resolved by discussion. For each of the identified studies included, the following data, when available, were extracted and recorded on the standard form: author and year of publication, number of patients, patient sex (male or female), age ($\leq$50 or $>$50 years), evolution of the disease, first symptoms, tumour location (mandible or maxilla), lymph node metastasis, histological grade (low, intermediate, or high; this was established by three of the authors who are specialists in oral pathology – FPF, HARP, and FSCP), treatment (radical surgery alone (tumour and margin excision), conservative surgery alone (local excision without margins or curettage), chemotherapy alone, radiotherapy alone, radical surgery + radiotherapy, radical surgery + chemotherapy, chemotherapy + radiotherapy, conservative surgery + radiotherapy, or radical surgery + chemotherapy + radiotherapy), and outcomes/follow-up (died of the disease, no evidence of disease, alive with disease, recurrence, and metastasis). The authors of the articles were contacted for possible missing data when necessary.

Analysis

Descriptive statistics are presented, including mean and standard deviation (SD) values, ranges, and numbers and percentages. Overall survival rates were estimated by Kaplan–Meier analysis and compared using a log-rank test. A P-value of <0.05 was considered statistically significant. Factors that were significantly associated with the prognosis of CHS in the univariate analysis were introduced stepwise into a Cox proportional hazards model to identify the independent predictors of survival. Data were analyzed using IBM SPSS Statistics for Windows, version 23.0 software (IBM Corp., Armonk, NY, USA).

Results

Literature search

The study selection process is summarized in Fig. 1. The database search strategy resulted in 8227 papers. Of these, 654 articles appeared in more than one database (duplicate articles) and were excluded. The abstracts of the remaining 7573 articles were screened against the eligibility criteria, following which 7393 were excluded for not being related to the topic. The full texts of the remaining 180 articles were evaluated, leading to the exclusion of 70 articles for the following reasons: did not report the mandible or maxilla as the primary site, did not report the histological grade or treatment, presented radiation-associated lesions, or did not meet the language criteria. Thus, a total of 110

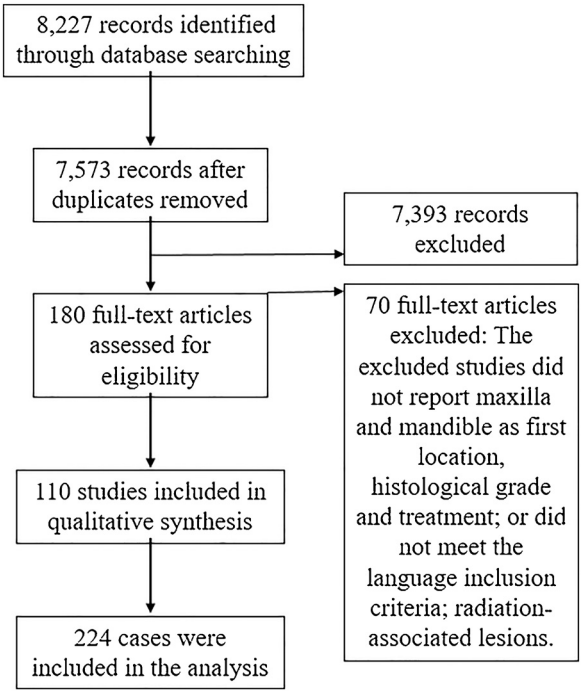

Fig. 1. Study screening process.

publications were included in the review (Table S1)[1–4,7,9–113].

Demographic characteristics and presentation

One hundred and ten publications reporting 224 cases of CHS were included in this review. Table 1 presents the demographic characteristics, clinical features, and survival analysis for CHS. The lesion was slightly more prevalent in males than in females, with a male to female ratio of 1.15:1. The mean age of the patients was 33.14 years (range 2–82 years); males were slightly older (mean age 33.38 years, range 9–73 years) than females (mean age 31.78 years, range 2–82 years). Figure 2 shows the distribution of CHS according to age, demonstrating that most subjects with CHS were in the second to fifth decades of life, with the greatest predominance in the third decade of life. The most commonly reported symptoms were swelling (50.4%), pain (20.5%), and facial asymmetry (19.6%), which developed over a mean duration of 12.72 months. The lesions were more prevalent in the maxilla in comparison to the mandible. Seventeen patients presented regional (lymph node) metastasis on clinical examination.

Imaging and histology

Preoperative imaging studies were reported for 149 of the cases. The imaging modality most commonly used was X-ray (panoramic, peri-apical, and occlusal), which was used in 77 cases (51.7%). Other imaging modalities reported included computed tomography (CT) ($n = 59$, 39.6%), magnetic resonance imaging ($n = 12$, 8.1%), and ultrasound ($n = 1$, 0.7%).

Biopsy results were explicitly reported in 171 cases. The most common results reported were conclusive biopsies in 154 cases (90.1%), benign cartilage in two cases (1.2%), initially chondroma in six cases (3.5%), and chondroma in nine cases (5.3%). Concerning the histological types, the most commonly observed was conventional (45.5%), followed by mesenchymal (36.2%), dedifferentiated (9.4%), myxoid (5.4%), juxtacortical (2.2%), and clear cell (1.3%).

Tumour characteristics and grading

The tumour size was reported following surgical excision in 87 patients. The average tumour size was 3.4 cm in greatest dimension (range 1–15.5 cm). Histological grading was reported in all 224 cases. Concerning the tumour grade, the most commonly diagnosed was low grade ($n = 105$, 46.9%), followed by high grade ($n = 102$, 45.5%) and intermediate grade ($n = 17$, 7.6%).

Therapy

The treatments used were radical surgery alone ($n = 126$, 56.3%), conservative surgery alone ($n = 23$, 10.3%), chemotherapy alone ($n = 3$, 1.3%), radiotherapy alone ($n = 5$, 2.2%), radical surgery with radiotherapy ($n = 30$, 13.4%), radical surgery with chemotherapy ($n = 10$, 4.5%), chemotherapy with radiotherapy ($n = 3$, 1.3%), conservative surgery with radiotherapy ($n = 11$, 4.9%), and radical surgery, chemotherapy, and radiotherapy ($n = 12$, 5.8%).

In addition, 13 patients underwent neck dissection associated with conventional treatment (seven radical surgery alone, four radical surgery with radiotherapy, one radical surgery associated with chemotherapy and radiotherapy, and one radiotherapy alone). Among the 13 patients who underwent neck dissection, six (46.2%) had regional lymph node metastasis: five with a high histological grade and one with an intermediate grade.

Patient outcomes and follow-up

The prognosis was specified in 169 cases. The mean follow-up was 64 months (SD 88 months, range 1–533 months). Of these 169 cases, 96 (56.8%) were alive with no evidence of disease, 64 (37.9%) had died of the disease, seven (4.1%) were alive with disease, and two (1.2%) had died of another cause at the time of follow-up.

Fifty-seven patients (25.4% had local recurrence at a mean interval of 30 months (range 2–132 months). Distant metastasis affected 29 patients (12.9%) after a mean time of 61 months (range 8–264 months) and involved the lungs (35.0%), vertebrae (17.2%), brain (6.9%), skull (6.9%), and ribs, deltoid, orbit, sternum, breast, scalp, vulva, pelvis, kidney, and liver (3.4% each). Among these, 22 patients died of disease and seven were alive with the disease at follow-up.

Survival analysis

Univariate survival analysis of the clinical variables and Kaplan–Meier analysis revealed that high-grade tumours ($P = 0.0013$), chemotherapy alone ($P = 0.0003$), recurrence ($P < 0.0001$), and metastasis ($P < 0.0001$) were statistically significant. Multivariate survival

Table 1. Demographic characteristics, clinical features, and survival analysis for chondrosarcoma of the jaw bones described in the literature ($N = 224$).

Variables		*P*-value	
		Univariate analysis	Multivariate analysis
Age (years), *n* (%)		NS	NS
≤50	185 (82.6%)		
>50	39 (17.4%)		
Sex, *n* (%)		NS	NS
Male	120 (53.6%)		
Female	104 (46.4%)		
Primary location, *n* (%)		NS	NS
Maxilla	118 (52.7%)		
Mandible	106 (47.3%)		
Lymph node metastasis, *n* (%)		NS	NS
Yes	17 (7.6%)		
No	207 (92.4%)		
Histological type, *n* (%)		NS	NS
Conventional	102 (45.5%)		
Mesenchymal	81 (36.2%)		
Dedifferentiated	21 (9.4%)		
Myxoid	12 (5.4%)		
Juxtacortical	5 (2.2%)		
Clear cell	3 (1.3%)		
Histological grade, *n* (%)		0.0013*	<0.0001*
Low	105 (46.9%)		
Intermediate	17 (7.6%)		
High	102 (45.5%)		
Treatment, *n* (%)[a]		0.0003*	0.002*
RS	126 (56.3%)		
CS	23 (10.3%)		
CT	3 (1.3%)		
RT	5 (2.2%)		
RS + RT	30 (13.4%)		
RS + CT	10 (4.5%)		
CT + RT	3 (1.36%)		
CS + RT	11 (4.9%)		
RS + CT + RT	13 (5.8%)		
Recurrence, *n* (%)		<0.0001*	0.001*
Yes	57 (25.4%)		
No	167 (74.6%)		
Distant metastasis, *n* (%)		<0.0001*	<0.0001*
Yes	29 (12.9%)		
No	195 (87.1%)		

NS, not significant.
* Significant; $P < 0.05$.
[a] RS, radical surgery; CS, conservative surgery; CT, chemotherapy; RT, radiotherapy.

analysis revealed that high-grade tumours, chemotherapy alone, recurrence, and metastasis were significant independent prognostic factors. Logistic regression showed that the odds of death (odds ratio) were 24 times higher for high-grade tumours than for low-grade tumours ($P < 0.0001$) (Fig. 3A). The odds of death were seven times higher for patients treated with chemotherapy alone than for patients treated with radical surgery alone ($P = 0.002$) (Fig. 3B). The odds of death among those who presented recurrence were 19 times higher than among those who did not present recurrence ($P = 0.001$) (Fig. 3C). Finally, the odds of death among patients who presented with distant metastasis were 16 times higher than among patients who did not present distant metastasis ($P < 0.0001$) (Fig. 3D).

Discussion

Demographic characteristics and aetiology

CHS is a malignant tumour that originates from primitive cartilage-forming mesenchyme[9–11]. CHS of the oral cavity are uncommon aggressive lesions, accounting for about 1% of all CHS[12,13]. Its aetiology appears to be related to the uncontrolled proliferation of Merkel cells (embryonic remains)[2]. With regard to CHS of the jaw bones, this appears to be the first systematic review of the literature on this subject.

This study found that CHS of the jaw bones presents most often in those in the age range of 11 to 50 years, with a peak incidence in the third decade of life. Previous studies have observed that CHS of the jaw bones tends to occur after 30 years of age[14–16]. The mean age of the 226 patients in this review was 33.14 years, and the mean age of male subjects was slightly higher than that of female subjects. Males were affected slightly more than females (male to female ratio of 1.15:1). It was also observed that the most prevalent symptom was swelling, which corroborates previously published information in the literature[17–22]. Further, the present literature review found that 52.7% of tumours affected the maxilla and 47.3% affected the mandible[23–25].

Histology

CHS grading for prognostic purposes is based on the histological characteristics of the lesion and indicates the histological grade[5]. There are several grading systems for CHS, the most popular being the World Health Organization Classification of Head and Neck Tumours, which was updated in 2017[5]. These grading systems assess a similar set of parameters and are point-based, assigning point values to increased cellularity, pleomorphism, multinucleation, and mitoses. Regarding the histological type, the conventional type presented most frequently (45.5%), which is in agreement with previous studies[7,16,26–28]. Concerning the histological grade, 105 (46.9%) were classified as low grade, 17 (7.6%) as intermediate, and 102 (45.5%) were classified as high grade tumours. Our results corroborates with other previous case series, which have shown a high number of low-grade tumour in CHS cases. The high number of high-grade tumours explains the association between histological grade and lower survival rate[3,16,27,28].

The differential diagnosis of CHS includes chondromas. Chondromas are composed of mature hyaline cartilage histologically resembling normal cartilage. Hypocellular areas contain evenly distributed, bland-looking chondrocytes in an abundant basophilic matrix. Chondrocytes have small, uniform and single nuclei surrounded by eosinophilic cytoplasm and there is usually only one cell per lacuna. Cellular pleomorphism, mitoses, and binucleated chondrocytes are absent. In contrast, CHS show variably increased

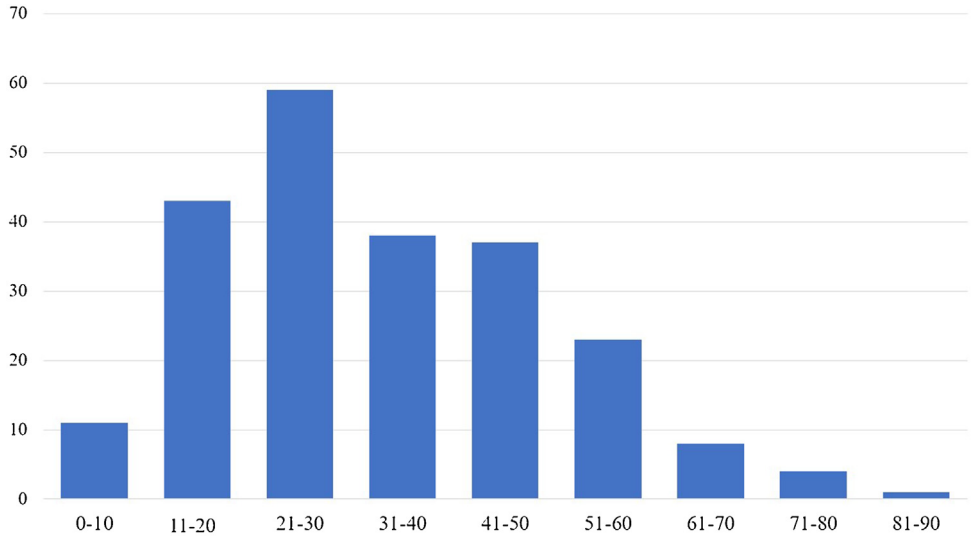

Fig. 2. Distribution of chondrosarcoma according to age.

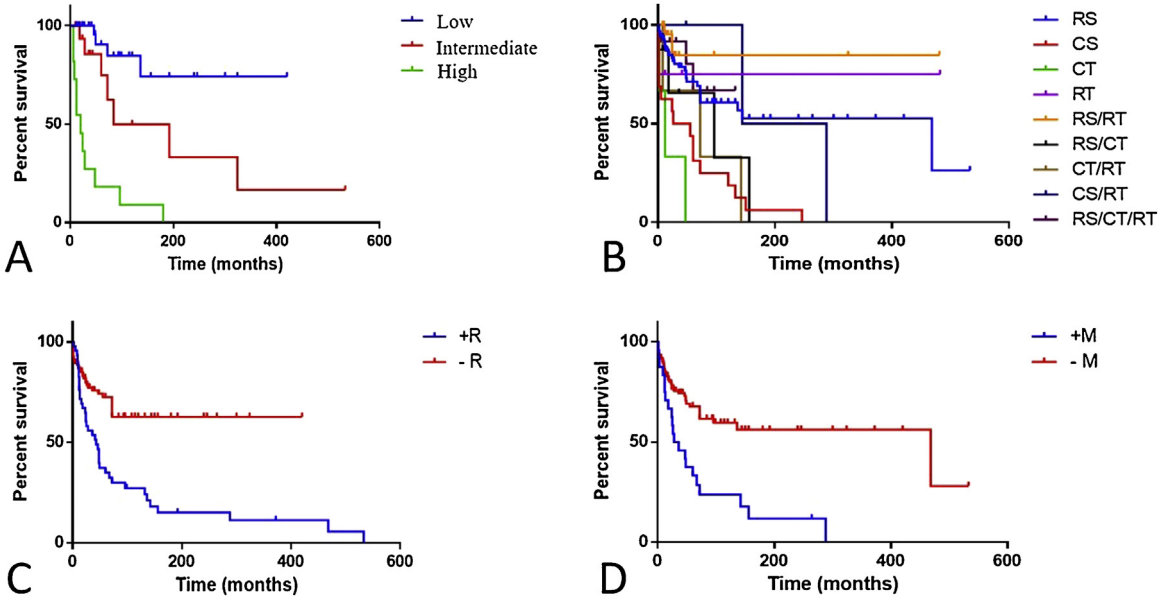

Fig. 3. Kaplan–Meier graphics showing statistically significant results for (A) histological grade ($P < 0.0001$); (B) chemotherapy ($P = 0.002$); (C) recurrence ($P = 0.001$); and (D) distant metastasis ($P < 0.0001$).

cellularity, pleomorphism, multinucleation, and mitoses, features useful to differentiate the lesions[5].

Treatment approach

It was observed that treatments involving radical surgery with margins presented a better prognosis when compared to conservative surgery (local excision without margins or curettage). This is consistent with other previous studies[29–31]. Thirteen patients underwent treatment modalities with associated neck dissection (seven radical surgery alone, four radical surgery with radiotherapy, one radical surgery associated with chemotherapy and radiotherapy, and one radiotherapy alone) and 46.2% of these patients had regional lymph node metastasis. Thus in this analysis, it was found that only a few articles reported the use of neck dissection, although among the 13 cases, six presented regional lymph node metastasis (five with high-grade tumours and one with an intermediate-grade tumour). Regional lymph node metastasis is not commonly found in association with head and neck CHS. However, Nakayama et al., in a review of the literature on regional metastasis in CHS of the larynx, observed that intermediate- and high-grade tumours tended to be associated with regional metastasis[114]. The present review results corroborate the results of Nakayama et al., but need to be confirmed, since the positive or negative occurrence of regional

lymph node metastasis was only described in a small number of cases.

Patient outcomes and follow-up

Regional metastasis and local recurrence were found in 7.6% and 25.4% of cases, respectively. It appears that regional metastasis is an unusual finding in CHS.

The mean follow-up period for the cases included in this review was 64 months, with 56.8% of patients alive with no evidence of disease, 37.9% dying from the disease, 4.1% alive with disease, and 1.2% dying of other causes. Thus CHS of the jaw bones presents a poor prognosis[4,26,32–34], and it should be emphasized that this lesion is characterized by possible late recurrence and metastasis: some patients have presented recurrence even after 132 months[35] and distant metastasis after 264 months[36]. Therefore, patients should be followed up for long periods after treatment

Prognostic factors

This study found that histological grade is a significant prognostic factor, although almost half were low-grade tumours[4,16,27,34,37]. Logistic regression showed that the odds of death were 24 times higher for high-grade tumours when compared to low-grade tumours[4,34].

Treatment protocols for CHS consist of radical surgery followed by chemotherapy and radiotherapy, depending on the oncologist's decision[4,7,11,26,34,38–40]. However, this analysis revealed that chemotherapy does not contribute to a favourable prognosis for the patient. It was found that radical surgery associated with radiotherapy was the best treatment protocol to improve patient survival[10,25,41–45]. The odds of death for patients who were treated with chemotherapy alone were seven times higher than those for patients treated with radical surgery associated with radiotherapy. An explanation for the resistance to chemotherapy may be the expression of the multidrug resistance 1 gene (P-glycoprotein), resulting in resistance to doxorubicin[115].

Furthermore, it was observed that patients who presented recurrence had a worse prognosis when compared to patients who did not present recurrence[1,16,25,26,37,46]. The odds of death among those who presented recurrence were 19 times higher than among those who did not present recurrence. Finally, another prognostic factor associated with patient survival was distant metastasis[7,16,32,34–36,47,48]. It was found that the odds of death among patients who presented distant metastasis were 16 times higher than among patients who did not present distant metastasis; the highest metastatic location was the lungs[16,32,47–49].

In conclusion, CHS in the jaw bones is a neoplasia of high aggressiveness and with a propensity for recurrence and distant metastasis. Furthermore, histological grade (high grade), chemotherapy alone as treatment, and the occurrence of recurrence and metastasis are all associated with a poor prognosis. Moreover, an effective follow-up is necessary to ensure the success of treatment, since recurrence and metastasis were observed after long periods of follow-up.

Funding

No funding was given to this study.

Competing interests

No conflict of interest is reported for this study.

Ethical approval

This study did not involve human or animal subjects or records.

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.11.006.

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