Clinical and Pathological Features of Osteosarcomas of the Jaws. A Retrospective Study

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Article

Clinical and Pathological Features of Osteosarcomas of the Jaws. A Retrospective Study

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Abstract: Introduction: Osteosarcomas of the jaw (OSJ) are rare tumors with a different behavior from osteosarcomas of other bones. This study aims to analyze the clinical, pathological, and therapeutic characteristics of this type of sarcoma. **Methods:** a retrospective observational study of cases diagnosed with OSJ registered at the "La Paz" University Hospital (Madrid). **Results:** Eight cases with a diagnosis of OSJ were obtained in a study period of 22 years (2000-2022). The mean age was 41 years. The distribution was 1:1 between the maxilla and mandible. Painful inflammation was the most frequent clinical manifestation. Conventional osteoblastic osteosarcoma was the most common. Survival at 5 years was 50%, while at 10 years, it decreased to 25%. **Conclusions:** OSJ differs from conventional osteosarcomas of long tubular bones. Surgery continues to be the mainstay of treatment; more studies are needed in which more standardized protocols can be proposed for adjuvant therapeutic management.

Keywords: osteosarcoma of the jaws; head and neck cancer; oral cancer; malignant bone tumors

Introduction

Osteosarcoma (OS) is a primary malignant tumor lesion of mesenchymal origin that shows osteogenic differentiation[1]. It mainly affects long bones (femur, tibia and humerus) [2]. Location in the maxillofacial territory is less common, around 6-7% of all OS [3]. Osteosarcomas of the jaws (OSJ) represent 6% of tumors affecting the jaws and less than 1% of all malignant head and neck tumors [4]. Unlike the rest of osteosarcomas whose presence is more common in children and adolescents, OSJ affect patients between the 3rd and 4th decade of life[5]. The mandible is the most affected bone in this location[6] and there is no predilection between males and females[7].

The etiopathogenesis of this type of neoplasia is uncertain, although chromosomal events that give rise to heterogeneous and complex chromosomal aberrations must be involved[8].

Osteosarcomas are most commonly present as central or intramedullary lesions in which conventional OS stands out as the most prevalent entity. This type of OS, in turn, can be divided into three subtypes according to its predominant cell differentiation and production of extracellular matrix: osteoblastic, chondroblastic, or fibroblastic, although they can present themselves conjointly in a mixed formation [9,10]. Other more unusual variants have been described, such as telangiectatic,

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small cell, epithelioid, and multinucleated giant cell-rich[9]. In addition to central lesions, OS can appear as bony surface or juxtacortical lesions (subdivided further into parosteal OS, periosteal OS, or surface OS) and as extraskeletal or soft tissue OS[6].

The OSJ clinic can be variable. Pictures of inflammation, paresthesia and pain are common, the latter between 3% and 8% of cases[11]. Other associated signs are displacement or tooth loss and misalignment of the removable dental prosthesis [11].

OS can have a primary origin or they develop secondarily. There are predisposing factors related to certain pathologies such as Paget's disease, Li-Fraumeni syndrome, Rothmund-Thompson syndrome type 2, Werner syndrome, Rapalidino syndrome, Bloom syndrome, intraosseous diseases such as fibrous dysplasia and ossifying fibroma, hereditary retinoblastoma and they can also originate in patients with prior radiotherapy treatment in the head and neck region[12,13].

The mainstay of treatment for OSJ is surgical resection of the tumor. Tumor infiltration-free margins are a prognostic factor for survival[14]. Other strategies include the administration of neoadjuvant chemotherapy or adjuvant therapy with chemo or radiotherapy[15], although there is no established protocol due to the low prevalence of this tumor lesion.

The prognosis of OSJ is better than that of OS of the extremities, with better survival data and fewer distant metastases[16,17].

The objective of this article is to review the cases of osteosarcomas of the jaws diagnosed and treated in the Oral and Maxillofacial Surgery Service of the "La Paz" University Hospital, in the period between 2000 and 2022, in order to study the clinicopathological, therapeutic and prognostic characteristics. We analyze the survival in this type of tumors and compare the data with other cases published in the scientific literature.

Patients and Methods

To carry out this retrospective observational study, a search was carried out in the database of the Oral and Maxillofacial Surgery Service and the Pathological Anatomy Service of the University Hospital "La Paz" in Madrid (Spain) of the cases diagnosed as osteosarcoma of jaws in the last 22 years. Data were collected regarding the clinical characteristics, location of the affected bone, type and quality of surgical treatment, administration of neoadjuvant and/or adjuvant treatment, pathological characteristics of the lesions, soft tissue invasion, recurrences and metastases, and data on the 5-year survival. To carry out the study, approval was obtained from the ethics committee of the Hospital "La Paz" IdiPAZ Research Institute (HULP: PI-5462) and in accordance with the Declaration of Helsinki [18].

Results

Characteristics of the patients

The total number of OSJ registered in the last 22 years was 8 cases. The age of the diagnosed patients was between 10 and 56 years, with a mean of 41 years, which represents 87.5% (n=7) women.

Regarding the origin of the OS, 5 were primary OS and 3 secondary OS. In the case of the latter, one of them was radiation induced after cavum cancer treated with chemotherapy and radiotherapy 11 years earlier, another case developed OSJ after having presented an ossifying fibroma in the same area 5 years earlier, and the third case debuted after retinoblastoma treated with chemotherapy (4 cycles of etoposide and carboplatin) and tomotherapy in a pediatric patient.

In relation to the clinical manifestations of the tumor, painful inflammation was the most prevalent symptom (62.5%), either mainly or associated with other symptoms such as bleeding, dental mobility and hypoesthesia of the inferior alveolar nerve. In two cases, the presentation was asymptomatic inflammation causing facial deformity (Figure 1).

With respect to the affected bone, there is a 1:1 relationship between the maxilla and the mandible, as well as the side where the lesion is located. A 50% distribution has been found for both the right and left sides (Table 1).

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Table 1. Patient characteristics.

Case	Age	Sex	Medical History	Signs and symptoms	Bone	Side
1	51	M	Pneumothorax at age 26	-Sensation of nasal obstruction -Progressive proptosis -Diplopia	Maxilla	Left
2	35	F	None	Painful swelling	Maxilla	Left
3	56	F	Cavum cancer (T2N2M0) at age 45. Treated with CT and RT	Painful swelling	Mandible (angle)	Right
4	56	F	None	Asymptomatic mass	Mandible (body and angle)	Right
5	49	F	Uterine myoma. Breast fibroadenoma	-Inferior dental nerve hypoesthesia -Painful swelling -Dental mobility of involved teeth	Mandible (body and angle)	Left
6	47	F	Maxilar ossifying fibroma at age 42	Asymptomatic mass	Maxilla	Right
7	10	F	Retinoblastoma at age 3. Treated with CT and RT. Right eye enucleation	Painful swelling	Maxilla	Right
8	31	F	Appendectomy at age 21	Painful swelling Oral cavity bleeding	Mandible (body and angle)	Left

M: male; F: female; CT: chemotherapy; RT: radiotherapy.

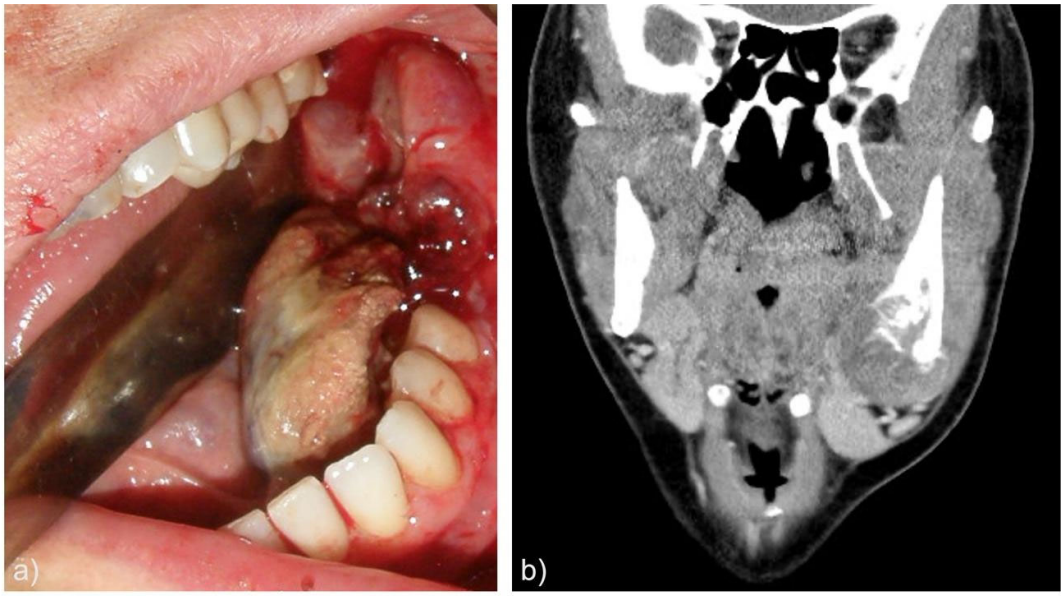

Figure 1. a) Intraoral clinical manifestation of tumor in the left mandibular molar area showing bleeding. b) CT coronal section image of the same lesion showing an area of osteolysis.

Pathological characteristics of tumor lesions

All registered cases were high-grade OSJ with a predominance of osteoblastic morphological pattern (n=3), followed by chondroblastic (n=2), epithelioid (n=2) and fibroblastic (n=1) patterns. According to the Broders classification[19], grade 4 was the most prevalent (2 cases of osteoblastic OSJ and 1 case of epithelioid OSJ) along with grade 3 (2 cases of osteoblastic OSJ and 1

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chondroblastic). In addition, data of a grade 3-4 fibroblastic OSJ and another case of grade 2-3 chondroblastic OSJ were found (Figure 2).

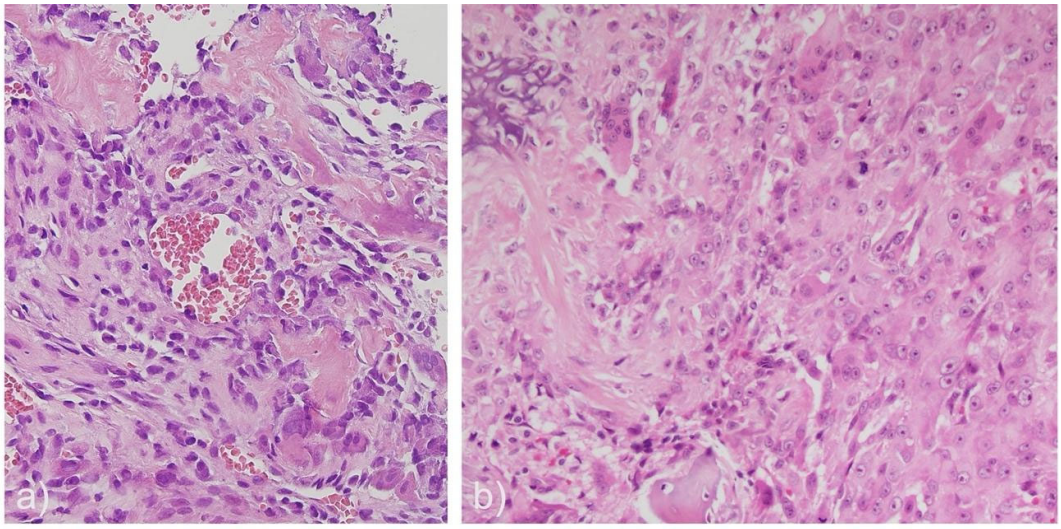

Figure 2. a) Conventional osteoblastic osteosarcoma (HE x400): there is a malignant mesenchymal cell proliferation with cytologic atypia, with variability in cell shape and size and anisokaryosis. Nucleoli are evident. The neoplastic cellularity varies in shape from polygonal to fusiform, and focally it is observed as producing calcified collagenous matrix (osteoid). b) Epithelioid osteosarcoma (HE x400): hypercellular malignant mesenchymal proliferation, which stands out in polygonal tumor cells with ample cytoplasm and nucleus with open chromatin and prominent nucleolus. Osteoid matrix is in direct relation with neoplastic cellularity.

In 50% of the cases, soft tissues were infiltrated; in case No. 2, during its recurrence.

Lymphovascular invasion was detected in two cases (cases No. 2 and 8). In case No. 2, it occurred in the recurrence of the tumor (Table 2).

Table 2. Pathological characteristics of tumor lesions.

Case	Histological morphology	Grade	Broders Classification	Soft tissue involvement	Lymphovascular invasion
1	Fibroblastic	High	Grade 3-4	No	No
2	Chondroblastic	High	Grade 3	No Yes (after recurrence)	No Yes (after 3rd recurrence)
3	Epithelioid	High	Grade 3	Yes	No
4	Osteoblastic	High	Grade 4	No	No
5	Osteoblastic	High	Grade 3	Yes	No
6	Chondroblastic	High	Grade 2-3	Yes	No
7	Osteoblastic	High	Grade 4	No	No

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8	Epithelioid	High	Grade 4	No	Yes

Treatment characteristics and results

The surgical treatment of choice in all cases was resection of the tumor by partial maxillectomy or hemimandibulectomy (Figure 3).

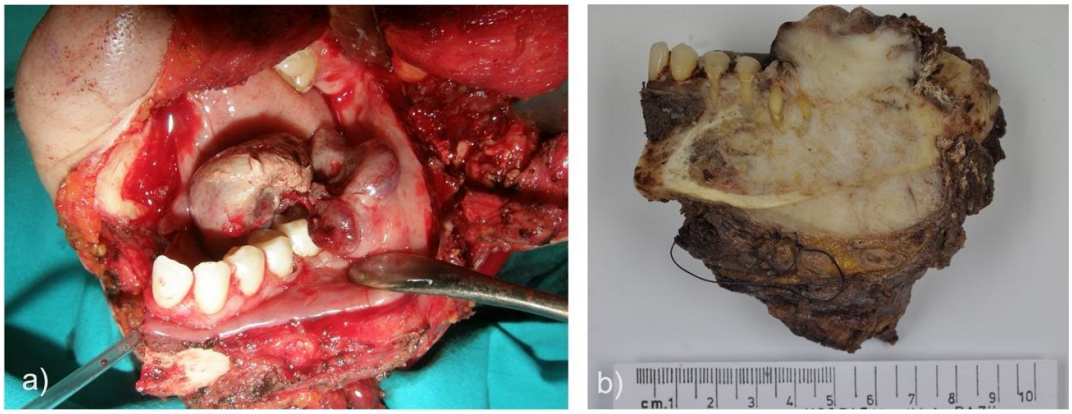

Figure 3. a) Image corresponding to left hemimandibulectomy with safety margins. b) Surgical piece for anatomopathological study.

The presence of tumor-free margins was identified in 6 cases, of which 3 corresponded to mandibular OSJ while 3 were maxillary OSJ. It is worth highlighting case No. 2, in which affected edges were found in the second local recurrence.

Neoadjuvant therapy was administered in 3 cases. In two cases, the same protocol using cisplatin and adriamycin was administered for only 1 cycle due to tumor progression. It was not possible to assess the percentage of necrosis of this in the histological study of the surgical piece. The third case, being a pediatric patient with a maxillary OSJ, was administered neoadjuvant therapy with the ISG-GEIS-OS2 protocol (Italian Sarcoma Group - Spanish Group for Research on Sarcomas-Osteosarcomas 2) consisting of the administration of methotrexate, adriamycin and cisplatin. In this case, 95% tumor necrosis was obtained.

Adjuvant therapy was administered in five cases initially and in another two cases after tumor recurrence (cases No. 2 and 3). In only one case, adjuvant therapy was not administered due to the presence of free tumor margins after surgical treatment and the absence of lymphovascular or soft tissue invasion (case No. 4). The most used protocol was that of cisplatin-adriamycin between 5 and 6 cycles. In 2 cases corresponding to epithelioid OSJ, due to the recurrence, progression and aggressiveness of the tumor, 1 cycle of the 2nd line chemotherapy with ifosfamide or ifosfamide-etoposide was used (cases No. 3 and 8). Radiotherapy (tomotherapy) was only administered together with chemotherapy (ifosfamide-cisplatin scheme) in one case for 5 cycles (case No. 1). The most common complication was local recurrence. It was observed in three cases (two in the mandible (cases No. 3 and 8) and one in the maxilla (case No. 2)). The epithelioid type was the most prevalent followed by the chondroblastic type. Specifically, in the case of maxillary OSJ with a chondroblastic pattern, there were 3 local recurrences of the same tumor (case No. 2). Distant metastases were only detected in one case, these being in the lung and liver. The Kaplan-Meier 20 method was used to calculate the cumulative probability of survival. In this survival study, there were only two cases in which the patient's death was recorded. Less than 1 year elapsed between diagnosis and death. There are two cases in which 0.58 years elapsed between the diagnosis of osteosarcoma and the end of the study, corresponding to the two cases of epithelioid OSJ who died in this period, while other patients have been in the study for 15.83 years, corresponding to a case of OSJ of osteoblastic type and other fibroblastic.

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Therefore, it can be established that at 2.5 years survival is 62%, while at 5 years it decreases to 50% and to 25% at 10 years (Figure 4).

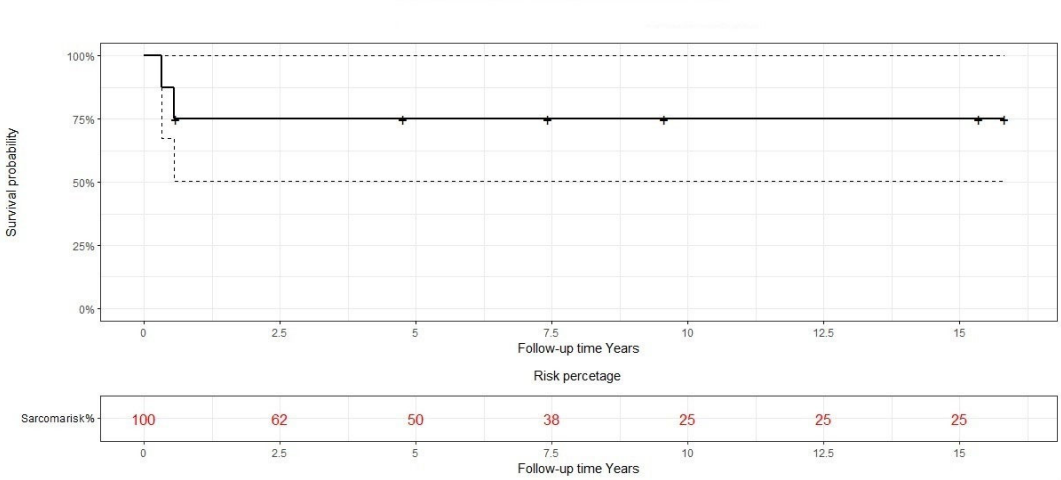

Figure 4. Kaplan-Meier survival diagram for osteosarcoma.

Table 3. Treatment characteristics and outcomes.

Case	Surgical treatment	Final surgical margin	Neoadjuvant therapy	Necrosis % post neoadjuvant therapy	Adjuvant therapy	Recurrences	Metastasis	Survival
1	Partial maxillectomy and eye enucleation	+	No	N/A	CTX: ifosfamide-cisplatin + RT: tomotherapy 6MV (5 cycles) / Epirubicin (3 cycles)	No	No	FOD 15 years
2	Partial maxillectomy	1st Surgery: - 2nd Surgery: - 3rd Surgery: n/c 4th Surgery: + 5th Surgery: n/c	CTX: cisplatin-adriamycin (1 cycle)	N/D	After 3º surgery (pregnant in 2º recurrence): CTX: cisplatin-adriamycin/ Methotrexate (5 cycles)	3 local recurrences	N/D	N/D
3	Hemimandibulectomy	-	No	N/A	In recurrence (no surgery decided) CTX: ifosfamide	1 local recurrence	No	Died
4	Hemimandibulectomy	-	No	N/A	No	No	No	FOD 15 years
5	Hemimandibulectomy	- (<1 mm)	No	N/A	CTX: cisplatin-adriamycin (6 cycles)	No	No	FOD 9 years

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6	Partial maxillectomy	-	No	N/A	CTX: cisplatin-adriamycin (5 cycles)	No	No	FOD 7 years
7	Partial maxillectomy	-	CTX: methotrexate-adriamicyn-cisplatin	95%	CTX: adriamicyn (1 cycle)	No	No	FOD 4 years
8	Hemimandibulectomy	+	CTX: cisplatin-adriamycin (1 cycle)	15%	CTX: ifosfamide-etoposide (1 cycle)	1 local recurrence	Yes	Died

Note: +: affected margins; -: free margins; n/c: not clear; N/A: not applicable; N/D: no data; CTX: chemotherapy; RTX: radiotherapy; FOD: free of disease.

Discussion

OSJ is a rare entity that presents a series of clinicopathological characteristics as prognostics that differentiate it from OS of the extremities. During the last 22 years, 8 cases of OSJ have been registered at the "La Paz" University Hospital. There are few large case series, most studies record between 8 and 28 cases in periods between 10 and 30 years[10,21–28]. The most extensive case series include between 74 and 114 cases, although in much longer study periods[29,30]. It is worth noting a recent study by Brown et al.[31] in which 164 cases are recorded, the series of cases being the most extensive in the literature. Although in our study the age range of diagnosis of the lesion was wide (from 10 to 56 years), with a mean age of 41 years, in general, the appearance of OSJ occurs in older patients, and their occurrence is common diagnosis between the 3rd and 5th decade of life, with a mean age of between 34 and 36 years. These data are consistent with those published in the scientific literature [10,23,25,28,30,32–34].

The vast majority of studies indicate that there is an equitable distribution between the maxilla and mandible, although with a slight predilection for the latter[32]. When correlating the age of appearance of the lesions with respect to the affected bone, Paparella et al.[29] observed a greater peak incidence in the maxilla in the 5th decade of life versus a similar distribution between young and older patients in OSJ with mandibular involvement. For Garrington et al. [32], this fact is explained by the presence of growth centers in the mandible that allow potential growth activity throughout life.

The distribution in terms of sex is not clear and there is controversy [10]. Mardinger et al.[26] pointed out that there is a slight predilection for the male sex; however, in our study we observed the opposite, with a clear predominance of women (87.5% of cases), although it is true that our sample of patients is smaller.

The most frequent clinical manifestation of OSJ is local inflammation accompanied or not by pain[28], as we have been able to corroborate in our study. However, other symptoms can be observed such as mobility or tooth loss, hypoesthesia of the dental nerve or visual disturbances such as proptosis or diplopia[24]. Radiologically, the findings that can be found are diverse. The appearance of a pattern in “rising sun rays” has often been associated as a pathognomonic image of OSJ; however, it is not exclusive to this type of lesions and it is not the most common radiological manifestation[29]. Several authors, in larger case series, have observed the presence of mixed radiological images, which requires an exhaustive differential diagnosis[29,32,35,36].

Histologically and to establish a certain diagnosis of OS, there must be the presence of a malignant mesenchymal tumor with bone or osteoid matrix production[37]. There is controversy regarding the higher prevalence of one histological type compared to another, since there are authors who describe the chondroblastic type as the most predominant in OSJ cases[23,26,28]. However, the osteoblastic type was the most common in our study, in accordance with what was reported by other authors[10,28,29,32,34]. Regarding fibroblastic differentiation, there is a greater consensus regarding

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its lower incidence in OSJ[21,23]. OS of the epithelioid type is a rare variant with only 6 cases published in the jaw region[7,38–42]. This variant, which was initially described by Scranton et al.[43] in 1975, is more prevalent in long bones and in men (2:1), and can present itself between the 1st and 7th decade of life, with a predilection for the mandibular bone. It is identified radiologically as poorly defined lytic lesions with the ability to show a periosteal reaction[38]. The presence of osteoid is a fundamental requirement for its diagnosis, although the amount present can be variable[7]. In our study, two cases were recorded with this morphological pattern in which an extensive neoformation of osteoid in socket was identified in close contact with the tumor cellularity. They corresponded to two women (56 and 31 years old) who presented OSJ with epithelioid origin in the mandible and maxilla, respectively, and who died within a period of less than 7 months. This aggressive behavior has already been described by other authors such as Okada et al.[39]. However, more studies are needed to analyze in a more extensive way the clinical behavior of this histological variant.

Special attention should be given to cases of OS that are diagnosed with a history of radiotherapy treatment to the head and neck[28]. This type of OS is generally of a high grade and usually has a worse prognosis[40]. In the case that we recorded, it was confirmed as a high-grade and more aggressive lesion.

There are conditions in which the risk of developing an OSJ is high. In patients with Li-Fraumeni syndrome or hereditary retinoblastoma, it has been possible to verify how there are chromosomal alterations in p53 and in the retinoblastoma genes located at 17p13 and 13q14 that increase this risk.[41]. OS can also develop in patients with Paget's disease. This quite rare condition since it usually affects only 1% of patients and with a greater predominance in the long bones[42].

Other predisposing factors such as ossifying fibroma must be taken into account[7]. In our study we observed the presence of an initial lesion diagnosed as ossifying fibroma that after 5 years debuted as chondroblastic OSJ. It is important to make a correct diagnosis since OS can be confused with benign fibro-osseous lesions such as fibrous dysplasia[34] and with other tumors such as osteoblastomas[44].

Regarding the treatment of OSJ, it should be noted that the protocol is not standardized and varies greatly between institutions[45]. However, surgical treatment that includes radical resection with wide free margins continues to be the main option and the one with the best prognosis for this type of tumor[22,24,25]. Achieving free margins is considered technically more difficult in the maxilla than in the mandible, with data ranging between 30% and 52% of affected margins after surgery[14,25,46]. According to what was recorded in our study, of the 4 patients with OSJ involving the maxilla, in 3 cases, free margins were achieved; however, after the local recurrence of one of them, the margins were affected.

Neoadjuvant (neoCTX) and adjuvant chemotherapy (CTX) are currently considered an essential complement to surgical treatment, especially in the management of high-grade osteosarcoma, especially in long bones[47]. However, the management of OS of the head and neck is not standardized and varies greatly between institutions[45]. There are no established protocols regarding the use of CTX, given the rarity of this type of injury and the lack of longitudinal data. Therefore, the treatment of OS of the head and neck has been largely guided by the treatment of OS of the long bones[48]. Since the introduction of adjuvant CTX in the treatment of the long-bone OS, the 5-year survival of these patients has increased considerably from 20% in the 1970s to 50% today. This increase is even more evident by up to 70% with the addition of cisplatin and ifosfamide to doxorubicin and methotrexate[49]. On the other hand, the use of neoCTX has also improved survival in OS of long bones, but its application in OSJ remains controversial. Recently, in a systematic review carried out by Khadembaschi*et al.*[50], it was analyzed if this type of treatment improves survival in OSJ and if it improves the percentages of tumor necrosis. The authors found no survival benefit for neoCTx versus surgery as the primary treatment modality in the treatment of head and neck osteosarcomas. Tumor necrosis percentages ranged from 0% to 76% (note that necrosis is effective when it is greater than 90%[50]). Even worse survival data may be found when surgical treatment is delayed[51]. In our study, the effectiveness of this type of treatment was observed in a single case, specifically a pediatric patient, with neoCTx achieving tumor necrosis data of 95%.

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The role of radiotherapy as a treatment for bone sarcomas, and specifically in OS, is limited and is also controversial as this type of tumor is radioresistant, which is why it is sometimes used as a treatment option when surgery is not possible[52]. The most common complication of this type of tumor in the location of the head and neck is local recurrence[34]. In our series, there are 3 cases with local recurrence. Due to its anatomical complexity and the difficulty of achieving free margins, the maxilla is usually the area in which most recurrences occur.

OSJs do not usually create metastasis and, if they do, it is in more advanced stages of the tumor lesion itself, unlike OS in the rest of the skeleton[53]. The differences regarding the embryonic origin of the affected bones may be related to this fact, since the craniofacial bones do not derive from hematopoietic progenitor cells but from neural crest cells[54]. In a recent study, it has been pointed out that the lower expression of the GLI1 gene in craniofacial OS can be interpreted as a lower activation of the Hedgehog (Hh) signaling pathway. This implies a greater polarization of the M1 protein and less activation of Hh in craniofacial OS, thus explaining the low incidence of OS metastasis in this location[55]. We have been able to corroborate this data as there was only one case of metastasis in our series.

Regarding the prognosis, it has been reported that the chondroblastic form has a better prognosis than other histological types[28,30,34,56,57]. Paparella et al.[29] have even registered a worse prognosis in this histological variant since it has been possible to observe greater morphological variations in the nucleolar organizer regions (AgNORs), being a marker of cell proliferation and showing a more aggressive behavior of this variant. In this regard, we have not found differences in terms of the conventional patterns (osteoblastic, chondroblastic and fibroblastic), but we have found differences in the epithelioid form, which is associated with a poor prognosis. There exists consensus in noting that high-grade injuries[28] and the ones with incomplete resection or local recurrence[26] have a worse prognosis. To these data, we must add that the presence of larger lesions is associated with lower survival[31].

The lower frequency of metastases in OSJs probably influences the survival results[58], with 5-year survival being around 77% for craniofacial OS while for conventional OS of the rest of the skeleton it ranges from 55% to 70%[48]. These data are highly variable due to the very small number of cases in the studies. In the specific case of OSJ, 5-year survival ranges from 45% to 74%[25,28,53,59,60]. In our study, the data are similar, since a survival of 50% was achieved in the same period. However, the limitations in the low number of cases in this study must be taken into account.

Conclusions

OSJs are rare lesions that differ from conventional long bone osteosarcomas in terms of the age range of onset, behavior with respect to adjuvant treatment, development of metastases, and prognostic and survival data. There are still discrepancies between the most prevalent histological forms of OSJ and those that provide a better prognosis.

Surgical treatment with margins free of tumor infiltration is the most decisive factor in terms of improving the prognosis and survival of OSJ. Few large case series have been reported that analyze in depth some characteristics regarding the most controversial points in the management of osteosarcomas, such as the effectiveness and response to adjuvant treatment. This makes more studies necessary in which more standardized protocols on therapeutic management can be proposed in this regard.

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Conflicts of Interest: The authors declare no conflict of interest.

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