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Chondrosarcoma of the Jaw: A Closer Look at its Management

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Chondrosarcoma is a malignant cartilaginous tumor rarely involving the mandible. The prognosis is generally poor depending on the degree of differentiation and the quality of the resection.

This article details the various methods of treatment and provides some clarifications on the clinical aspects as well as the therapeutic approach.

Chondrosarcoma is classified by the World Health Organization (WHO) as a malignant tumor with pure hyaline cartilage differentiation[1] characterized by the formation of cartilage, but not of bone, by tumor cells.[2]

Chondrosarcoma accounts for approximately 10% to 20% of all primary malignant bone tumors[3] and, excluding multiple myeloma, represents the second most common primary bone malignancy after osteosarcoma.[3]

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The term chondrosarcoma describes a heterogeneous group of tumors with varying morphology and clinical history including conventional chondrosarcomas that constitute 90% of all chondrosarcomas and rare subtypes that constitute the remaining 10%.[4] Another large distinction is made between primary chondrosarcomas that arise in a previously normal bone and secondary chondrosarcomas that arise in a benign precursor such as an enchondroma or an osteochondroma. Conventional chondrosarcomas include primary central, primary periosteal (juxtacortical, a rare variant of conventional chondrosarcoma arising on the surface of metaphysis of long bones), and secondary (in Ollier's disease and Maffucci syndrome); dedifferentiated, clear cell, and mesenchymal constitutes the rare subtype group. Table 1 shows the main clinicopathologic features that distinguish these subtypes. It is notable that chondrosarcoma is usually more aggressive in younger individuals than in adults.[5] The incidence of involvement of head and neck sites varies from 5% to 12%,[6,7] with larynx,[8] thyroid cartilage, and arytenoids being the most common sites of occurrence. However, chondrosarcomas can occur in virtually all other sites of the craniofacial compartment in which cartilage is found, such as the mandible, maxilla, and maxillofacial skeleton (nose and paranasal sinuses), as well as at the base of the skull and in the nasopharynx.[6,8-10] In the head and neck, chondrosarcomas are slightly more common in men than in women, and primarily occur in the fourth to seventh decades of life.[8]

Etiology

The etiology of chondrosarcomas still remains unclear, and their management controversial. The myriad of proposed methods of treatment include radical surgical resection,[11] local curettage,[12] cryosurgery,[13] chemotherapy,[14] radiotherapy,[15] and immunotherapy.[16]

It is known that chondrosarcoma of the maxillofacial region is extremely rare. Fourteen cases in India[17] and 35 cases of chondrogenic tumor over a period of

Table 1. CLINICOPATHOLOGIC ASPECTS OF CHONDROSARCOMAS

CHS Histotype	Demographic	Clinical Characteristics	Grading
Primary	Adulthood	More than 75% in trunk, proximal humerus, and femur (acetabulum is the most common region) Five-year survival is about 90% for grade 1 CHS and around 50% for combined grade 2 and 3 CHS	Usually grade 1 or 2 Before establishing a diagnosis of grade 3 CHS, a chondroblastic osteosarcoma has to be ruled out
Secondary	Younger than in primary CHS	Arises in osteochondroma or in enchondroma 2% risk of developing CHS in solitary osteochondroma Risk is 5% to 25% in osteochondromatosis	In osteochondromas, usually grade 1; in enchondromas, variable grades
Secondary in Ollier's disease and Maffucci syndrome	Patients are born with disease; incidence of CHS increases with age	Can involve any bone In Ollier's disease, multiple enchondromas In Maffucci syndrome, multiple enchondromas and hemangiomas 25% to 30% risk of developing CHS	Usually grade 1
Dedifferentiated	Sixth decade	10% of all reported CHS Prognosis is dismal; 90% of patients are dead within two years	CHS with a biphasic pattern showing two distinct components with an abrupt demarcation: *1*) a well differentiated chondroid tumor (enchondroma or more frequently a grade 1 CHS) and *2*) a high-grade nonchondroid sarcoma (more frequently a "malignant fibrohistiocytoma" and less frequently fibrosarcoma, osteosarcoma and rhabdomyosarcoma)
Clear cell	Third decade	2% of all reported CHS Male to female ratio is 3:1 Nearly always involves the epiphysis of long bones, proximal femur in 50% of cases	Grade 1 Bland clear cells and hyaline cartilage If incompletely resected, recurs in about 90% of cases Recurrence is associated with metastasis
Mesenchymal	Any age; peak is in second and third decades	3% to 10% of all primary CHS Widespread distribution; most common sites are neural axis, cranial base, midface, jawbones, ribs, ilium, and vertebrae High rate of local recurrence Protracted clinical course with metastasis observed even after 20 years Mesenchymal CHS in the jaw have a more indolent course	Sarcoma with a biphasic pattern composed by an undifferentiated small cell round cell tumor (simulating Ewing's sarcoma but without 11;22 translocation) showing a hemangioperycitomatous pattern, and areas of well-differentiated hyaline cartilage Treated with an Ewing's sarcoma protocol

Abbreviation: CHS, chondrosarcoma.

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50 years in Japan[18] have been published. Paddison and Hanks[19] have indicated that primary involvement of the maxilla by this tumor is particularly rare, whereas others claim the same frequency of involvement between the maxilla and mandible.[20,21] Pindborg reported only 1 case of chondrosarcoma in an eleven year period in Denmark underlying the very low prevalence of this neoplasm.[22] Interestingly, individual cases of maxillary chondrosarcomas have been reported.[23,24] However, very few sizeable studies of chondrosarcomas of the mandible have been published.[25]

Table 2. REPORTED PRESENTING SYMPTOMS OF CHONDROSARCOMA OF THE JAW

Tumor	Pain	Dental Symptoms	Nasal Symptoms	Headache
Swelling	Significant Sharp	Loose teeth	Nasal obstruction	
Mass	Dull	Separated teeth	Epistaxis	
		Malocclusion		
		Gingival bleeding		
		Recent extraction		

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The predilection of chondrosarcoma for the mandibular symphysis, coronoid, and condylar processes may be explained in part by embryological issues. In fact, the bones of the symphysis, coronoid, and condylar processes ossify endochondrally, whereas the corpus and ramus of the mandible undergo intramembranous ossification. Thus, it has been suggested that chondrosarcomas arise from primitive mesenchymal cells, or from embryonic remnants of the cartilaginous matrix.[26,27]

Diagnosis

Clinically, these tumors may present with pathological fractures or are discovered incidentally on radiographs. More frequently, symptoms such as gingival bleeding and paresthesia of the lower lip occur, as well as tooth mobility and/or loss of teeth (Table 2). On other occasions, pain of referred dental origin causes the patient to consult a dentist. These lesions may appear radiographically as osteolytic, with radi-

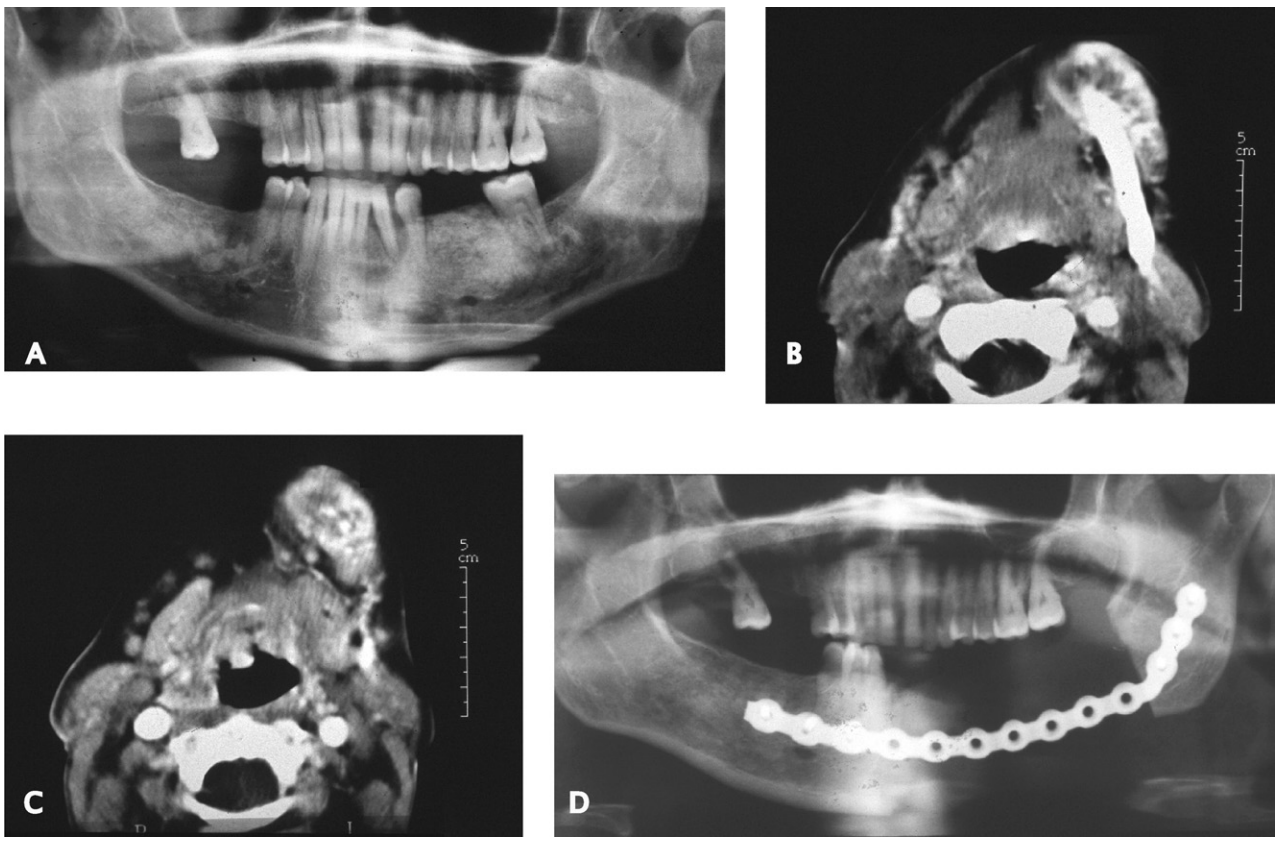

FIGURE 1. *A,* The preoperative orthopantomogram shows an ill-defined chondroid lesion along the left side of the mandibular symphysis with cortical breakthrough and periostitis. *B,* The preoperative axial computed tomography scan of the same patient shows a solid tumor with chondroid matrix (devoid of osteoid matrix) and a thick cartilaginous cap with areas of calcification and aggressive features as detailed on the radiograph as well as soft tissue extension. *C,* Computed tomography scan of the same patient demonstrates local recurrence of the aggressive chondroid tumor with similar imaging features status post curettage of the primary tumor. *D,* Follow-up orthopantomogram of the same patient after subsequent wide local resection and reconstruction without evidence of local recurrence.

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olucent shadows with a wide zone of transition and irregular/indistinct borders.[27-29] Alternatively, they may demonstrate an ill-defined cloud-like matrix with the calcified "whorls and arcs" typical of a chondroid matrix plus or minus aggressive features such as endosteal scalloping, cortical disruption, periostitis, and/or soft tissue mass effect (Fig 1A). Computed tomography (CT) may be very helpful in determining the presence (or lack) of chondroid matrix and the osteoid matrix as well as the extent of the lesion including infiltration of adjacent structures and tissues that may be poorly visualized on routine roentgenograms (Figs 1B,C).[30,31] This is a particularly important issue because many osteosarcomas of the jaw frequently have chondroblastic differentiation which may cause confusion with chondrosarcomas.[32,33] It has been suggested that CT or magnetic resonance imaging (MRI) should be used to determine nodal stage of head and neck tumors because clinical estimation of nodal involvement is incorrect in up to 25% of cases.[34] CT and MRI are complementary techniques in assessing bone cancers. CT is excellent in characterizing tumor matrix and cortical/periosteal involvement. MRI is important in the assessment of bone marrow extension and the involvement of the adjacent soft tissue structures.[35] Radiographic features of central and peripheral chondrosarcomas may vary depending on circumstances, such as presence or absence of tumoral calcification, patterns of bone destruction, encroachment on the cortex, and presence of periostitis. High grade (aggressive) chondrosarcomas may show large areas of irregular or absent calcification of the tumor and a poorly defined boundary between normal and abnormal bone. Bone scans show increased uptake of radionuclide in cases of central chondrosarcomas and reveal metabolically active areas in peripheral chondrosarcomas. Whole body bone scans can also be used to identify metastatic foci. Absence of uptake essentially rules out malignant transformation of an osteochondroma. CT scanning is valuable in showing the extent of the tumor and may be able to define the thickness of the cartilaginous cap in peripheral chondrosarcomas. CT is more sensitive than MRI for the detection of calcifications. MRI defines the full extent of tumor and is particularly useful in anatomically complex areas. Chondroid lesions in general are of inhomogeneous or homogeneous high signal intensity on T2-weighted spin-echo images. Intravenous administration of gadolinium compounds typically shows focal or diffuse enhancement of signal intensity on T1-weighted fat-suppressed sequences.

Diagnosis can only be established by histopathologic examination. However, histologically it can be a difficult task to differentiate benign and low-grade malignant chondrogenic tumors due to the subtle differences between the 2 lesions. Chondrosarcomas are usually more cellular than benign enchondromas, the hypercellularity may not be diffuse and it may be limited to scattered areas. Chondrosarcomas when compared with benign chondroid lesions show more cytological atypia, expressed by the variation in size and shape of neoplastic chondrocytes, along with nuclear hyperchromasia, pleomorphism, and frequent binucleation. Myxoid changes with nonhomogeneous and "stringy" appearance are also frequent in chondrosarcomas, whereas necrosis and increased mitotic activity are more frequent in higher-grade tumors.[36] The single most important feature differentiating a malignant chondroma from a benign tumor is the permeative pattern of the former with true infiltration of the cortical and or the medullary bone, and /or extension into surrounding soft tissue; radiology plays a determinant role in the evaluation of this feature. This is particularly important when dealing with chondroid tumors of small bones of hand and foot where hypercellularity, hyperchromasia, binucleation, and myxoid changes also can be present in benign tumors.[1,37] Prognostic factors include histologic grade, tumor necrosis, mitotic activity, and myxoid changes. Histologic grading is the single most important factor in predicting local recurrence and rate of metastasis. Table 3 shows the principal parameters to evaluate in grading chondrosarcomas.

Table 3. GRADING

Grade 1	Grade 2	Grade 3
Hypercellular tumors with monomorphic hyperchromatic nuclei and occasional binucleation	Moderately hypercellular tumors Moderate nuclear pleomorphism and hyperchromasia	High cellularity Prominent cellular pleomorphisms and nuclear atypia
Abundant matrix		Decreased matrix
Low mitotic count		Mitoses and necrosis frequent
Necrosis absent		
Cytologically indistinguishable from benign enchondromas		

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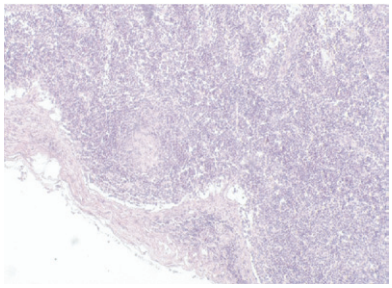

FIGURE 2. Low grade chondrosarcoma. Hyaline matrix with pleomorphic neoplastic chondrocytes, including a binucleate cell in lacunae.

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Five-year survival is about 90% for grade 1 chondrosarcomas and around 50% for combined grade 2 and 3 chondrosarcomas. Occasionally, chondrosarcomas show the coexistence of various histologic grades in the same tumor; it is appropriate in these cases to quantify the different grades by percentage.[38]

Differential diagnosis must be based on studying the cellular structure, rather than the calcified portion of the tumor (Fig 2).[27,29] In this respect image-guided biopsy may help in treatment planning. In this disease the cartilaginous cells are large, irregular, and have hyperchromatic nuclei, and the matrix shows a transition from myxoid to chondroid tissue.[9,39] At a later stage of the disease process, the tumor may become more immature and of a higher histological grade, with a more fibrous, myxomatous, or mesenchymal-appearing matrix.[40]

Treatment

Because of the rarity of chondrosarcoma of the jaw there are no established evidence-based treatment protocols. For this reason, many of the current treatment strategies for this disease have been extrapolated from protocols developed and tested for chondrosarcomas of other more typical locations outside of the head and neck region or other types of sarcomas. Chondrosarcoma is generally treated with a multimodal approach: wide en-bloc resection,[11,41-44] local curettage,[12] cryotherapy,[12] chemotherapy,[14] radiotherapy,[15,19,45] and immunotherapy.[16] Treatment depends on the size of the tumor and extent of the lesion. Adequate surgical resection remains the gold standard for the treatment of the jaw chondrosarcoma.[11] For patients with resectable lesions it represents the primary modality of treatment.[12,46,47] The resection area must be as wide as possible. Surgical clear margins are very important for favorable prognosis and for a decreased risk of recurrence (Figs 1C,D). Ideal initial resection includes bone margins of 2 to 3 cm surrounding the lesion even when the cortex is intact.[46] This surgical approach often requires extensive ablative procedures that can compromise major functional and esthetic elements and necessitates the performance of complex bone reconstructive techniques (Fig 3).[44] The intralesional excision–curettage of large lesions, combined with a powerful local adjuvant radiation therapy, can be advocated in these cases even if this approach is not curative.[12,42] Cryosurgery is suggested for the treatment of grade 1 chondrosarcoma.[13,48,49] Many studies seem to agree that the risk of local recurrence is limited in cryosurgically treated grade 1 chondrosarcoma. Additionally, functional results are improved when compared with those obtained with marginal or wide excisions. From an oncological point of view, results obtained from the combined approach of cryosurgery and intralesional excision are similar to those of marginal excision and even better than those of wide excision of grade 1 chondrosarcoma.[13] The use of cryosurgery can be associated with complications such as infection, embolism, and neuropathy; infection is the most common associated risk in the head and neck region, especially when cryosurgery is combined with reconstructive procedures. Even though surgery is the treatment of choice for this disease, high recurrence rates have been observed with surgery alone and, as a result, combined treatment of surgery with radiation and/or chemotherapy has been suggested. In summary, the real role of these adjuvant therapies is still controversial, because there have been few reported cases with sufficient follow-up to confidently determine outcomes. Some studies have shown better

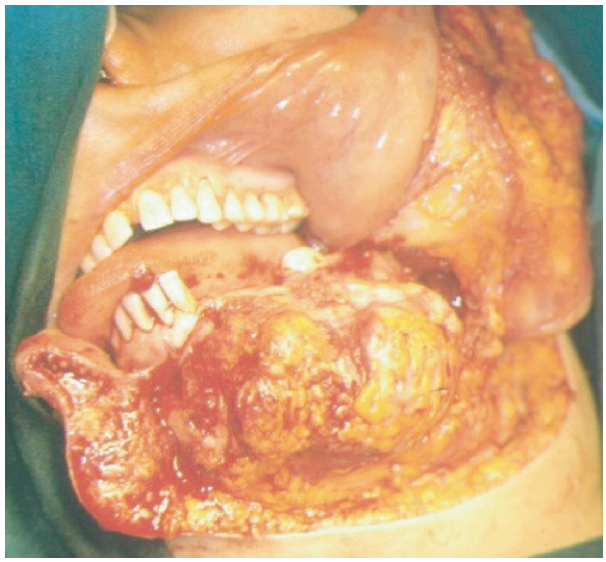

FIGURE 3. Surgical access showing the chondrosarcoma in the left mandible.

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prognosis using combined treatments of surgery and irradiation[15,19,45]; others indicate that the benefits of this combined treatment remain unproven.[28,29,43] Many authors believe that chondrosarcoma is a radioresistant tumor because of a prolonged response time to irradiation[12,50] which appears to not provide any survival benefits.[41] Irradiation therapy could have a role in some instances, such as in the case of incompletely resected or inoperable tumors.[42,44] Some authors suggest that the combination of radiation therapy and chemotherapy is synergistic in reducing the viability of tumor cells that may disperse during surgical procedures and to control rapidly growing tumors as neoadjuvant therapy before surgery.[19,43]

Because of the improved outcome of adjuvant chemotherapy combined with surgery in cases of sarcoma of the jaw [46] some investigators have taken into consideration the use of this regimen also in chondrosarcoma of the jaw. However, because of the lack of specific data, the efficacy of this type of treatment is not well established, even if the majority of the studies indicate no significant therapeutic benefits from the use of chemotherapeutic agents.[16,41,42,45,46,51,52] Questions persist, however, regarding the use and timing of chemotherapy before or after surgery. Most surgeons would agree on neoadjuvant chemotherapy in cases of chondrosarcoma, because it is intuitive that clear margins would otherwise be unobtainable without undue morbidity. Crawford et al,[14] using chemotherapy as neoadjuvant treatment, suggested that although combined chemotherapy did not decrease the size of the tumor, it inhibited tumor growth and spread. The use of chemotherapy postoperatively is also controversial in the case of clear pathological margins. Of course, information such as tumor distance from the margins and histological grading is useful in the decision-making process.[46] Although, in general, chondrosarcomas have been thought to be resistant to chemotherapy, a great interest has emerged about its use in metastatic disease and in dedifferentiated forms. Mitchell et al[53] suggested the possible role of chemotherapy for the dedifferentiated forms; the dedifferentiated component is a high grade spindle and/or pleomorphic sarcoma (Table 1), and a (at times dramatic) positive response has been documented for other high grade sarcomas treated with chemotherapy. However, Dickey et al[54] have discussed the inherent risks of chemotherapy and concluded it is not beneficial in improving the long-term survival or distant metastasis control. This illustrates that a more effective adjuvant method needs to be implemented; molecular genetics represents a field of investigation that may hold hopes for this aim. Recent studies in the molecular biology of chondrosarcoma have pointed to the role of progressive acquired molecular abnormalities in the evolution of enchondromas to low grade chondrosarcomas and from these to high grade chondrosarcomas; other pathways seems to be involved in the de novo development of chondrosarcomas from "normal" cartilage. Like other tumor types, chondrosarcoma demonstrates a peculiar antigenicity that may support an immunologic etiology. Several molecular targets have been identified for future development of new adjuvant therapies;[1,4] some of these may include hormonal antiestrogenic therapy,[4,55] antiangiogenesis treatment with selective cyclo-oxygenase-2 (COX-2) inhibitors,[4,56] and inhibition of parathyroid hormone-like hormone (PTHLH) pathway with Bcl-2 antisense therapy.[4,57] More studies are needed to confirm the hypothesis of the previously mentioned multistep genetic model for the arising and evolution of chondrosarcomas and to explore the possibility in the future of immunotherapy in the treatment plan of this disease.[16]

In our opinion, the treatment plan for chondrosarcoma of the jaws, like treatment plans for most of the malignant tumors of the oral and maxillofacial region, is restricted to radical surgery which provides patients with the greatest chance of long term survival and cure. High-energy irradiation, chemotherapy, immunotherapy, and cryosurgery may be useful as adjuvant forms of therapy in rare instances, but have not yet been extensively studied relegating them to secondary lines of therapy for chondrosarcomas of the jaw.

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