Chapter 12

# Osteosarcoma of the Jaw: Classification, Diagnosis and Treatment

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http://dx.doi.org/10.5772/67564

**Abstract**

Osteosarcomas are rare, highly malignant, bone tumors defined by the presence of malignant mesenchymal cells producing osteoid or immature bone. Osteosarcomas of the jaws are extremely rare, representing about 7% of all osteosarcomas and 1% of all head and neck malignancies. An accurate diagnosis, usually facilitated by chemotherapy (CT), MRI and biopsy, is required in order to define the stage of the disease and plane the adequate treatment. Aggressive surgical resection and advanced technique reconstruction are the mainstay of treatment, as the single most important factor for cure is radical resection. Clinical outcomes can be improved by a multimodal strategy combining surgery with neo-adjuvant and adjuvant chemotherapy in selected cases, and adjuvant radiotherapy in the absence of clear margins.

**Keywords:** jaw osteosarcoma, sarcoma, reconstructive surgery, chemotherapy, radiotherapy

## 1. Introduction

Osteosarcoma is the most common malignant primary tumor of bone, with an estimated incidence of approximately two cases per million persons per year. It accounts for 40–60% of all primary malignant bone tumors [1–4].

Its peak incidence is in the second to fourth decades and is more frequent in fast growing bones. When the diagnosis of osteosarcoma is made earlier than the second decade or after the cessation of skeletal growth, an association with other osseous abnormalities should be

searched. Indeed, osteosarcoma can arise in the context of a genetic predisposition or underlying abnormalities such as Paget disease or fibrous dysplasia. Later in life, it can present in previously irradiated bone [3, 5].

The histopathological characteristic of osteosarcoma is the presence of aggressive malignant mesenchymal cells producing osteoid or immature bone.

Osteosarcoma of the jaw (JOS) is extremely rare, representing about 7% of all osteosarcomas and 1% of all head and neck malignancies [1, 2, 5–9].

The mandible and maxilla are almost equally involved. Unlike long-bone osteosarcoma, JOS is diagnosed more frequently in men than in females and presents about two decades later [5].

Microscopically, approximately 50% of JOS are chondroblastic or osteoblastic. In the first case, a minimal production of osteoid matrix is present which, on the contrary, prevails in the latter [1, 3, 6, 7].

If untreated, the prognosis of JOS is extremely poor. Surgery has a crucial role as the ability to treat a patient rest on a combination of aggressive surgical resection and advanced reconstructive techniques. The single most important factor for definite cure is radical resection [5, 7–23] with particular attention to achieve clear margins, a difficult task in relation to the complex anatomy of the maxillofacial region [13, 14, 20–23].

Many factors affect the prognosis of osteosarcoma. The most studied are histological subtype, grade, tumor size, patient age and response to chemotherapy (CTx) [5, 9–11, 24, 25].

From studies carried out on long bone sarcomas, it is well known that the most important prognostic indicator is the grade of CTx-induced necrosis, classified on the basis of viable tumor found in the surgical sample after resection [10, 11, 25].

Increasing necrosis with neoadjuvant chemotherapy positively correlates with efficacy, but this association has been recently questioned [26] and has to be further assessed in the future.

The clinical and biological behavior of long-bone and jaw osteosarcomas slightly differs. Head and neck osteosarcomas have a tendency to recur locally, and frequent symptoms are swelling at the site of disease, facial dysesthesia and loosening of the teeth. They give rise to distant metastases less frequently than osteosarcomas of the extremities [1, 2, 5, 7, 8, 12], which usually reveal their presence with swelling and pain, but sometimes even with disseminated symptomatic disease.

At present, a multimodal approach consisting of a combination of surgery, CTx and/or radiotherapy (RTx), has gained strong consideration, and the prognosis has progressively improved over the years.

Nonetheless, the role of CTx and RTx is still evolving [13, 14, 19–23, 27].

Considering that micrometastases can be present at diagnosis, perioperative CTx can offer some potential benefit in order to improve loco-regional control and to reduce the occurrence of distant metastases. The degree of histologic response to CTx provides the treatment team with useful information about tumor chemosensitivity. The role of RTx is still not clear in the

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multimodal strategy. It must be strongly considered in case of positive margins or high-grade tumors [12, 13, 21, 28].

For patients who are not candidates for surgery because of choice or associated comorbidities, RTx is an alternative for local control. Patients with poor performance status or seriously ill should be offered optimal supportive care in order to control symptoms and preserve quality of life.

## 2. Epidemiology, risk factors and genetics

Osteosarcoma is a disease of childhood and adolescence peaking in the second decade of life. Worldwide, a second smaller peak has been recognized later, in the seventh decade of life. The incidence rates in childhood and adolescent osteosarcoma range between 3 and 4.5 cases/million population/year, whereas the rates in older persons are estimated to be about 1 to 2 cases/million population/year for persons aged 25–59 years and 1.5–4.5 cases/million population/year for persons over the age of 60 [29].

A higher incidence of childhood osteosarcoma has been reported in Italy, Latin America, Sudan and Uganda compared to other populations around the world. In individuals 25–59 years of age, the incidence is greatest in Blacks, whereas over the age of 60, osteosarcoma incidence is greatest in Whites. Higher rates in the elderly have been reported in the United Kingdom and Australia [29, 30].

When considering a wide range of ages, males are affected with osteosarcoma more frequently than females. Bone growth, hormonal changes and growth during puberty may be involved in osteosarcoma etiology, partly explaining the slightly higher overall incidence in males.

Osteosarcoma occurs most frequently in the lower long bones, whereas the jaws are unusual primary sites of disease. Maxilla and mandible osteosarcoma (equally affected) represent about 7% of all osteosarcomas.

In order to find etiological relationships between environmental exposures and rare cancers such as osteosarcoma, a few studies have been carried out, limited by small sample sizes. Indeed, the cohorts to be studied are usually too large to identify significant correlation in a population where the disease is a rare one.

Among risk factors for osteosarcoma, fluoride exposure has been ascribed to contribute to bone cancer etiology, but subsequent studies did not confirm this finding [31].

Data from recent studies provided no evidence that higher levels of fluoride in drinking water lead to greater risk of either osteosarcoma or Ewing sarcoma.

A predisposition has been found in young patients affected by genetic syndromes characterized by somatic or germline mutations. Inherited cancer predisposition syndromes are a heterogeneous group of disorder in which higher rates of cancer in general and osteosarcoma in particular are noted. An increased risk of osteosarcoma has been associated with the Li-Fraumeni syndrome, caused by autosomal dominant germline mutations in TP53, or with

retinoblastoma, caused by mutations in the RB1 tumor suppressor gene. A common feature of the genes involved is their crucial role in normal cell growth and development, apoptosis and DNA repair. Mutations of suppressor genes lead to uncontrolled proliferation and malignant transformation. Also, patients with germline mutations in DNA helicase genes have increased rates of bone sarcoma, as demonstrated in the rare Rothmund Thomas syndrome, Werner syndrome and Bloom syndrome [32].

In more advanced age patients, two risk factors have been recognized: radiation therapy and Paget's disease.

Previous irradiation increases the risk of developing osteosarcoma, mainly for patients who received RTx for leukemia/lymphoma, but no correlation has been found with respect to low dose radiation received for medical diagnostic tests.

Paget's disease of bone is a relatively common metabolic bone disorder characterized by uncoupled bone remodeling, depending on abnormalities in osteoblast and osteoclast communication. The incidence of osteosarcoma secondary to Paget's disease is not known, but it is estimated to be about 1% [33].

This association accounts for about half of the osteosarcomas reported in elderly patients.

Despite many efforts, the etiology of osteosarcoma remains largely unknown. Epidemiologic studies have provided many important associations with puberty and height or disorders of bone growth and remodeling, but this bulk of knowledge is mainly confined to long-bone osteosarcomas. Data on JOS are less conclusive, so further research is still needed in order to improve our diagnostic and therapeutic approach.

## 3. Pathology

Osteosarcoma is a primary malignant bone tumor in which the mesenchymal neoplastic cells produce osteoid or immature bone. Therefore, the observation of osteoid is the key for the diagnosis of osteosarcoma [**Figure 1**].

### 3.1. Histotypes

Histologically, osteosarcoma is divided into the central (intramedullary) and peripheral (surface) subtypes.

The main type of central osteosarcoma is the conventional osteosarcoma, which is represented by a broad spectrum of morphologies. Besides the production of osteoid and immature bone, histological features are the presence of neoplastic cells showing anaplasia with epithelioid, plasmacytoid or spindle aspects and the growth with a permeative pattern, filling the marrow space surrounding and eroding pre-existing trabeculae [**Figure 2**]. Depending upon the predominant type of extracellular matrix present, conventional osteosarcoma is classified histopathologically into osteoblastic, chondroblastic and fibroblastic subtypes [34].

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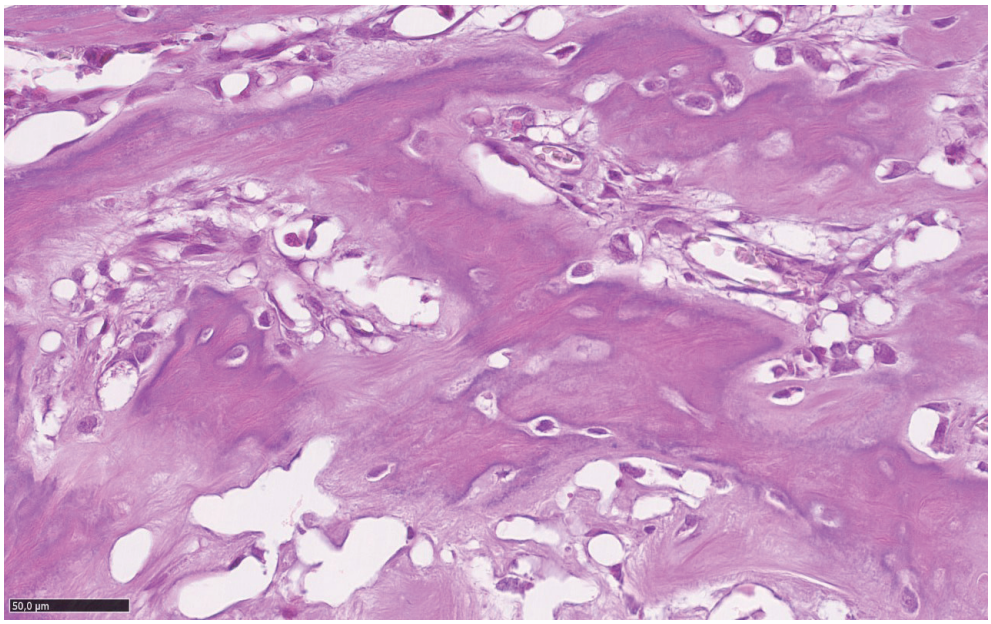


**Figure 1.** Picture showing osteoid and immature bone in OS.

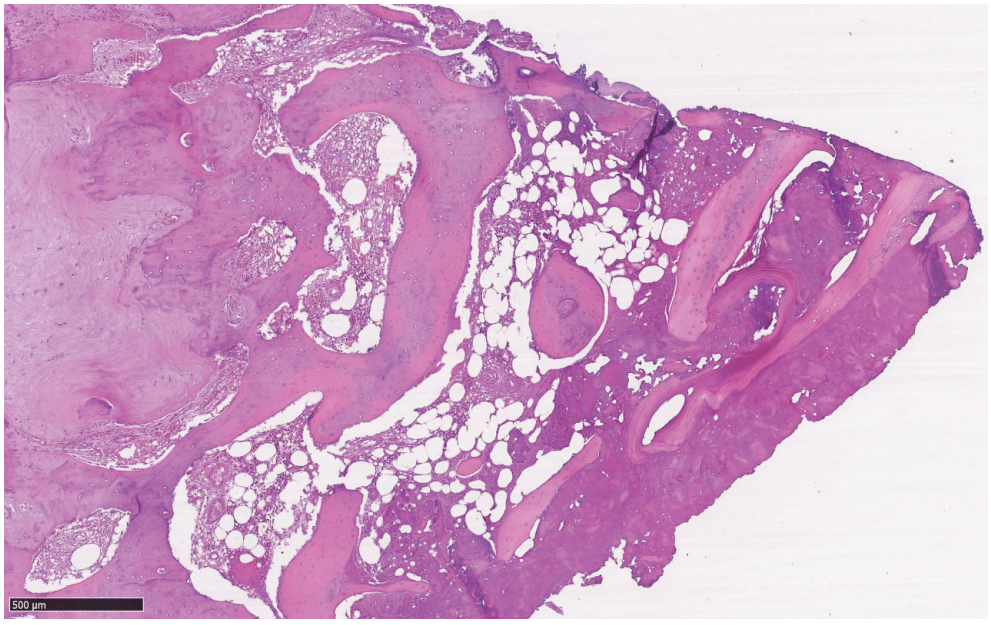


**Figure 2.** OS with a permeative pattern, filling the marrow space.

The osteoblastic subtype consists of osteoid or immature bone surrounded by haphazardly arranged fibroblast-like or epithelioid cells. The chondroblastic variant shows areas of atypical hyaline chondroid tissue. The cartilage may be the dominant component or scattered throughout the tumor. The fibroblastic subtype shows spindle-shaped neoplastic cells, characteristically arranged in herringbone pattern-like fibrosarcoma. The formation of tumor osteoid differentiates this variant of osteosarcoma from fibrosarcoma.

The World Health Organization (WHO) [35] in 2013 reported other osteosarcoma histotypes such as low-grade, giant cell rich, osteoblastoma and chondroblastoma-like, epithelioid, clear cell types, telangiectasic and small cell (**Table 1**).

The peripheral osteosarcomas are represented by parosteal, periosteal and high-grade surface osteosarcomas.

JOS is relatively rare and the majority of them arise de novo but some of them may develop in bone affected by Paget's disease, fibrous dysplasia, bone infarcts, chronic osteomyelitis, trauma, viral infection, exposure to high-dose radiation, metallic implants, joint prostheses in genetic syndromes such as Li-Fraumeni syndrome, hereditary retinoblastoma and RTx [36].

The JOS histotypes are the same as the conventional ones in long bones but differ from them in predominant differentiation pattern [38].

Most series of JOS report predominantly chondroblastic differentiation subtypes, more often myxoid [**Figure 3**].

| | |
|---|---|
| Low-grade central osteosarcoma | |
| Conventional osteosarcoma | Chondroblastic |
| | Osteoblastic (including sclerosis) |
| | Fibroblastic |
| | Giant cell rich |
| | Osteoblastoma-like |
| | Chondroblastoma-like |
| | Epithelioid |
| | Clear cell |
| | Secondary |
| Teleangectasic osteosarcoma | |
| Small cell osteosarcoma | |
| Parosteal osteosarcoma | |
| Periosteal osteosarcoma | |
| High-grade surface osteosarcoma | |

**Table 1.** Osteosarcoma classification (WHO 2013).

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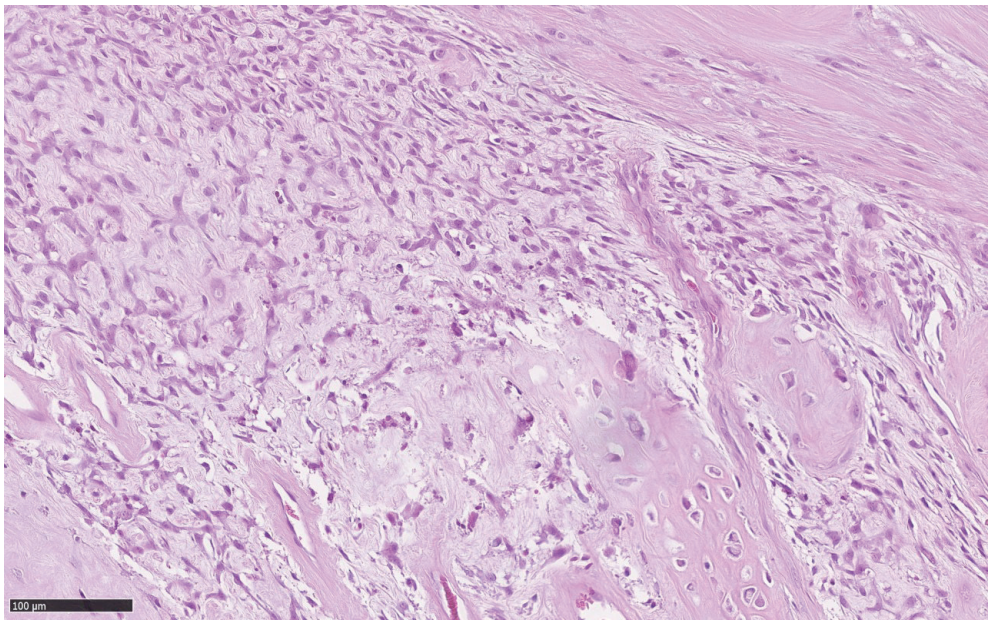


**Figure 3.** OS with myxoid aspect.

Mardinger et al.—for example—reported the highest prevalence for chondroblastic OS (42%), osteoblastic osteosarcomas being lesser (33%) in JOS [37].

In other series, the osteoblastic pattern was predominant, followed by the chondroblastic pattern [39, 40].

Finally, there is no consensus regarding the main differentiation patterns (osteoblastic and chondroblastic), and more often JOS display a more heterogeneous histotype as Bennett et al. [41] and Nissanka et al. [42] also pointed out.

The histologic heterogeneity of osteosarcoma highlights the need for histology to be supported by clinical and radiographic data for a correct diagnosis [33].

Other less frequent but not less important histological subtype of central JOS is the low-grade central osteosarcoma (LGCO)(1–2% in JOS). This is a well-differentiated osteosarcoma consisting of spindle cell fibroblastic proliferation with low cellularity, no significant atypia, low mitotic figures and a variable osteoid production. The most important feature of LGCO in long bones, and also in the jaw, is its similarities with benign lesions, first of all with fibrous dysplasia. Histological characteristics, including cellularity amount, cellular atypia and mitotic activity rate, are not very helpful, and the interpretation of small biopsies is very difficult, unless there are definite radiographic evidences showing the presence of an aggressive lesion. An excisional biopsy specimen must contain a large and adequate part of the tumor tissue together with surrounding tissue, with tumoral cells infiltrating into the bone marrow, cortical destruction by tumor and tumor invasion into soft tissues. Curettage should not be performed [43].

The peripheral osteosarcomas occasionally affect the jaw. The most frequent is parosteal (or juxtacortical) osteosarcoma which represents less than 5% of all osteosarcomas. It is well differentiated and characterized by spindle cell stroma with minimal atypia and rare mitotic figures separating irregular trabeculae of woven bone, arranged in a parallel manner. With time, the trabeculae often coalesce and form a large mass of solid bone. About 40–50% of parosteal osteosarcomas exhibit foci of cartilage. Approximately 10–25% of parosteal osteosarcomas dedifferentiate into high-grade osteosarcoma with a corresponding worsening of prognosis [34, 44].

### 3.2. Immunohistochemistry

Immunohistochemical detection of MDM2 and CDK4 may provide useful diagnostic tool [34, 45].

Recently, Yoshida et al. reported that the combination of MDM2 and CDK4 by immunohistochemical analysis shows 100% sensitivity and 97.5% specificity for the diagnosis of low-grade osteosarcoma. They concluded that MDM2 and CDK4 immunostains reliably distinguish low-grade osteosarcoma from benign lesions, and their combination may serve as a useful adjunct in this difficult differential diagnosis [46].

However, Tabareau-Dalanlande et al. noted discordant results, with 33% of ossifying fibromas and 12% of fibrous dysplasias exhibiting MDM2 amplification by qRT-PCR but no cases exhibiting MDM2 overexpression by immunohistochemistry. These investigators also showed amplification of an MDM2 neighbor, RASAL1, in all the fibro-osseous lesions with MDM2 amplification but in none of the low-grade osteosarcomas studied [47].

A recent study illustrated that some high-grade JOS is differentiated/dedifferentiated osteosarcomas harboring overexpression and amplification of MDM2. Juvenile ossifying fibromas can rarely evolve into giant cell-rich high-grade osteosarcomas and are characterized by a RASAL1 amplification [48].

### 3.3. Grading

Cellularity is the most important criterion used for histological grading. In general, the more cellular a tumor is, the higher is the grade. Irregularity of the nuclear contour, enlargement and hyperchromasia of the nuclei are correlated with grade. Mitotic figures and necrosis are additional features useful in grading. The grade is divided into low grade (G1) and high grade (G2) [34].

The surface osteosarcomas are further divided into parosteal, well-differentiated (low-grade), periosteal low- to intermediate-grade and high-grade surface osteosarcomas [49–51].

Although there have been various attempts to grade histological osteosarcomas, the reproducibility is poor [40].

### 3.4. Staging

Staging incorporates the degree of differentiation as well as local and distant spread, in order to estimate the prognosis of the patient. The universal Tumor Lymph nodes Metastasis (TNM) staging system is not commonly used for sarcomas because they are unlikely to metastasize in lymph nodes.

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The American Joint Committee on Cancer (AJCC) System for bone sarcomas still recognizes four stages: Stage I and II for low grade and high grade without metastasis, respectively, Stage III for "skip metastasis" and Stage IV for metastatic sarcomas.

The system used most often to formally stage bone sarcomas is known as the Musculo-skeletal Tumor Society (MSTS) or Enneking system [52].

It is based on the grade (G) of the tumor, the local extent of the primary tumor (T), and whether or not it has metastasized to regional lymph nodes or other organs (M). The extent of the primary tumor is classified as either intra-compartmental (T1), meaning it has basically remained in place, or extra-compartmental (T2), meaning it has extended into other nearby structures. Tumors that have not spread to the lymph nodes or other organs are considered M0, while those that have spread are M1 [53].

In summary, low-grade tumors are defined as stage I, high-grade tumors as stage II and metastatic tumors (regardless of grade) as stage III.

### 3.5. Prognosis

Osteosarcoma of the jaw is usually considered clinically as intermediate grade tumors and most authors point to the favorable prognosis of JOS compared with long-bone osteosarcomas. Paget's disease-related JOS is, however, aggressive tumors [40].

The two main prognostic criteria of JOS are tumor size and resectability at presentation [54].

Positive margins are strongly associated with poor prognosis; unfortunately, marginal excision is unavoidable in some JOS due to anatomic difficulties [15].

Complete resection of tumors involving the maxilla can be technically challenging, so local recurrence is more frequent in maxillary than mandibular osteosarcomas and, considering both sites, more common than the occurrence of distant metastases [5, 15, 16].

Death is usually secondary to local tumor extension with neural and vascular infiltration [38].

## 4. Clinical features

Males are affected by JOS slightly more frequently than females. Median age is between 30 and 40 years. Maxilla and mandible are equally involved, and the prognosis is similar [23].

The duration of symptoms before presentation is typically about 3–6 months. The most common presenting symptoms are swelling at the site of disease, which is almost universally present, and local pain, reported by approximately 70% of the patients. Other complaints are numbness and facial dysesthesia (32%), loosening of the teeth (14%), trismus, limitation of mouth opening, headache and nasal obstruction or bleeding. Patients rarely complain about systemic symptoms like fever, asthenia or weight loss. A few patients have no symptoms at presentation, and their tumors can be discovered incidentally by radiography. Physical examination can demonstrate a painless, firm mass, fixed to the underlying bone covered with normal tissue. Lymph nodes involvement, either cervical, supraclavicular or axillary, is unusual [22].

At first presentation, metastatic disease is present in 5% of the patients. This is less than in patients with appendicular skeleton osteosarcoma. The lungs are the most frequently involved sites.

Plain radiography and CT scan may demonstrate the presence of lytic lesions or mixed lytic and sclerotic lesions. Intraosseous tumors generally present as a poorly defined combination of radiodense and lucent lesions. In some cases, the cortex is invaded and eroded by the tumor, which extends into the soft tissues, frequently eliciting a periosteal reaction. Sometimes, the tumor grows expanding the bone but without violating the cortex. In other cases, the tumor surface is homogeneously radiodense and well demarcated from the soft tissues, resembling an osteoma. In the purely lytic lesions, the diagnosis may be difficult, as osteosarcomas mimicking hollow areas without new bone formation cannot be differentiated from metastatic disease radiographically.

Some laboratory parameters, such as alkaline phosphatase or lactate dehydrogenase (LDH) serum levels, can be increased in a few patients. Although they do not correlate reliably with disease extent, they may have negative prognostic significance [34].

## 5. Treatment

The prognosis of patients affected by JOS depends on few recognized risk factors. The most important is the achievement of clear margins with surgery. Furthermore, older age is statistically associated with decreased survival [55]. CTx with four or more agents used in a multimodality strategy is associated with a trend toward better disease-free (DFS) and overall survival (OS) [5].

On a multivariate analysis model recently reported, age (hazard ratio [HR], 1.03; 95% CI, 1.02–1.04 [$P < 0.001$]), surgery (HR, 0.31; 95% CI, 0.16–0.60 [$P < 0.001$]) and stage at presentation (HR, 1.37; 95% CI, 1.10–1.71 [$P = 0.006$]) were found to be independent predictors of OS. Moreover, age (HR, 1.03; 95% CI, 1.02–1.05 [$P < 0.001$]), surgery (HR, 0.22; 95% CI, 0.09–0.56 [$P = 0.001$]), tumor size (HR, 1.01; 95% CI, 1.00–1.01 [$P = 0.003$]) and stage at presentation (HR, 1.34; 95% CI, 1.01–1.76 [$P = 0.04$]) were found to be independent predictors for disease specific survival [56].

Age under 30 years, early stage (IA-IIB), and surgical treatment significantly correlated with a better prognosis.

### 5.1. Surgery

As it is the case for other skeletal locations, surgery is a mainstay of osteosarcoma treatment also in the head and neck region. The rationale and principles of surgical treatment of JOS depend on the location of the tumor [23, 57].

Obtaining disease-free resection margins is of course imperative, to avoid the risk of local recurrence.

Nevertheless, this goal is even more difficult to reach when dealing with head and neck osteosarcomas, since resecting few millimeters more often means endangering pivotal

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functional structures, with a noticeable decrease in the patients' quality of life. While intraoperative determination of resection margins might represent a useful tool in other head and neck malignancies, osteosarcomas do often pose a significant challenge for the surgeon: Intraoperative pathological examination does not indeed allow for the assessment of bone margins. Only soft tissue margins can be assessed through the intraoperative consultation [58].

Because of the anatomical complexity of the region, tumor resections are occasionally incomplete. Local recurrences and intracranial invasion have long been reported as the major causes of treatment failure due to incomplete neoplasm resection [59].

For the head and neck region, appropriate preoperative information is usually derived from the combined study of CT scans and MR imaging, both with contrast [**Figure 4**].

The CT scan allows a better assessment of the bone involvement and extension (better hard tissue definition), whereas the MR imaging aims at defining with considerable accuracy the soft tissue involvement [60].

While whole body bone scintigraphy and chest CT scan area advised for the initial staging [61], there is no general consensus for the routine implementation of whole-body MR and positron emission tomography (PET)/CT or PET/MR, which are under evaluation both for staging and treatment response evaluation [62].

According to the histopathological diagnosis, obtained through the biopsy, and the extension of the neoplasm, the multidisciplinary team indicates the best treatment for the patient [57].

When dealing with high-grade osteosarcomas, the best curative option is represented by a multimodal treatment. Multimodality increases DFS from the disappointing 10–20% of surgery alone to a solid > 60%. On the other hand, the treatment of low-grade central and parosteal osteosarcomas can rely on surgery alone, provided a complete assessment of their metastatic potential [63].

Irrespective of the treatment plan, whether monomodal or multimodal, the principles of surgery remain just the same. Effective treatment requires wide resections, as disease-free margins are associated with lower risk of local recurrence and higher overall survival. Nevertheless, despite the best staging and the most delicate and careful reconstruction techniques, it comes naturally that the 3 cm resection margin usually advocated for sarcomas of other sites (e.g., long bones sarcomas) is unthinkable when dealing with the head and neck structures. If we take into account literature reports, safety margins for head and neck osteosarcoma vary, from the observation of Granados-Garcia, who suggests a resection tailored on tumor size in the head and neck region [64], to the 1 cm minimal resection margin suggested by Ketabchi [65] [**Figure 5**].

As previously anticipated, despite obtaining adequate margins being the first goal of surgery, resection of head and neck osteosarcomas requires a careful balance between effective surgery and function-sparing procedures [25].

Surgical planning and the technical execution should be based on the expectation of performing a functionally effective reconstructive surgery [12, 25].

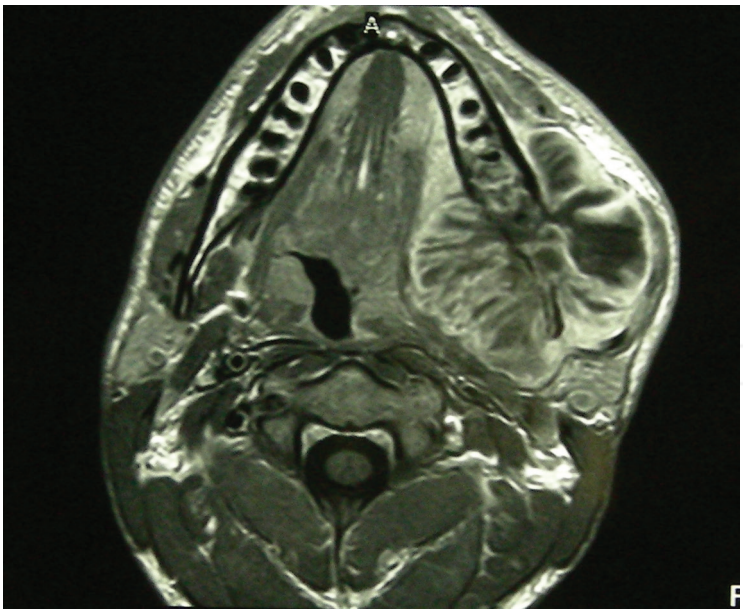


**Figure 4.** Preoperative MR imaging scan showing the extension of the mandibular neoplasm.

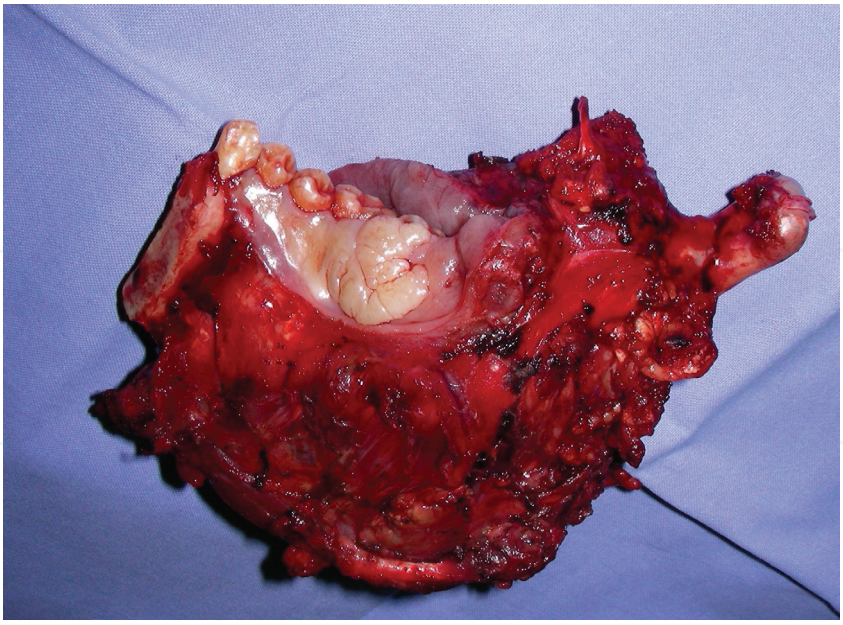

**Figure 5.** Intraoperative view of the mandibulectomy specimen after resection.

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The management of tissue defects in head and neck oncological surgery relies on loco-regional flaps for small deficits or on free microvascular flaps and metal prosthetics plates for large resections. When dealing with JOS, it is of the utmost importance that such free flaps allow also for transposing bony tissues. These technically refined procedures, which are usually performed in tertiary referral centers, enable not only a functional and aesthetic reconstruction but also a better future prosthetic rehabilitation of the patient's dentition, which has a relevant and natural role not only in food processing but also in social relationships [63].

Different flaps have already been proposed including the iliac crest microvascular free flaps [64], radial forearm flap with partial radius inclusion [67] and scapula osteocutaneous flap [68].

Nevertheless, the fibula flap, introduced by Taylor and colleagues [69], has become the most utilized in mandibular reconstruction due to its favorable characteristics (co-harvesting with multiple skin paddles, harvesting as a neurosensory flap, optimal form restoration and acceptable functional results), high rate of success and low rate of complications in both recipient and donor sites [**Figures 6**, **7**].

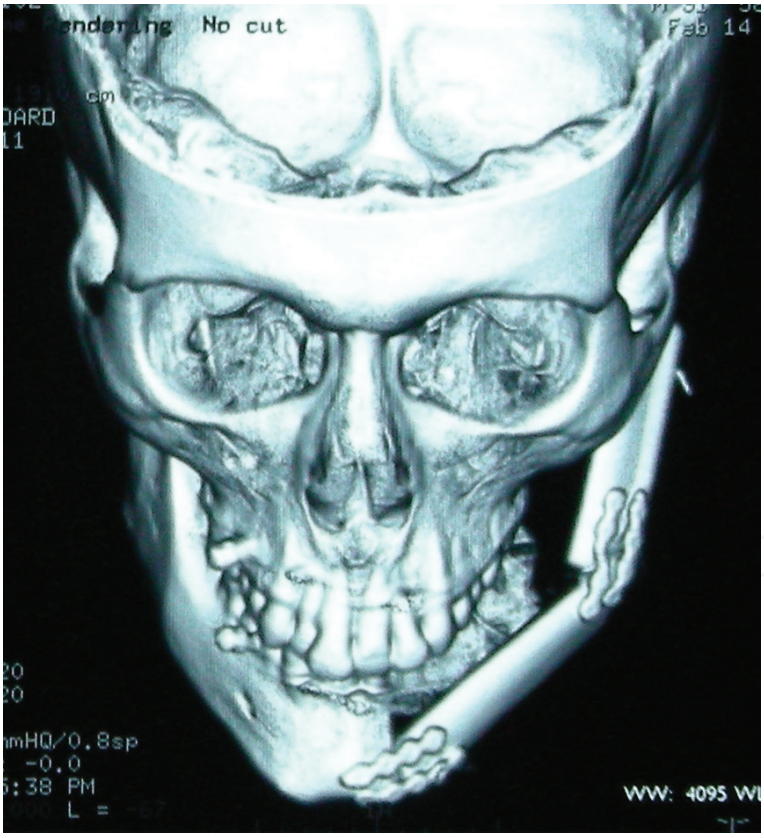


**Figure 6.** Postoperative 3D CT scan showing mandibular reconstruction with fibula free flap.

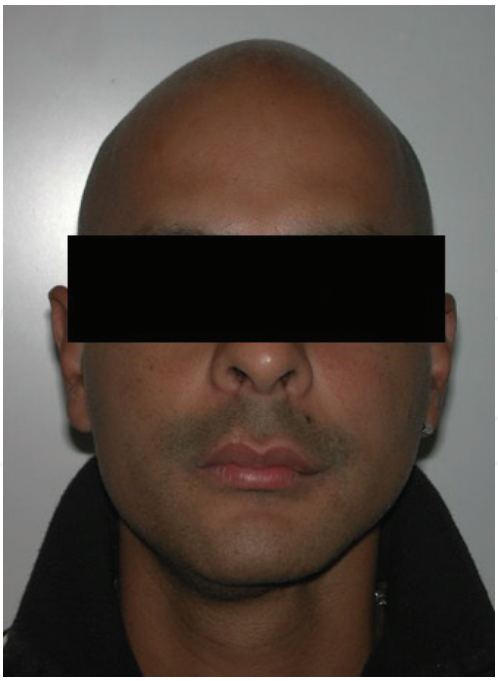

**Figure 7.** Frontal postoperative picture showing the excellent symmetry of the face.

These impressive reconstructions have been further enhanced by the progressive implementation of techniques such as virtual surgical planning using computer-assisted modeling [70].

This technique allows reconstructing defects with astonishing anatomical faithfulness not only with free flaps but also with custom-made synthetic plates which are the standard reconstruction method in elderly or compromised patients. It has to be noted that reconstruction, despite being almost unavoidable in order to obtain a good quality of life, makes the radiologic follow-up more complex, due to the increased effort required by the specialist in differentiating normal, neoplastic and grafted tissues. These features must be taken into account when planning the procedure and informing the patient, and radiologic follow-up examination should be conducted in specialized structures with dedicated personnel.

Large bone and soft tissue free margins are more easily achievable in osteosarcomas involving the mandible than in sarcoma of the upper jaw, were posterior control of resection and may be extremely difficult. This is particularly true when upper jaw malignancies involve the skull base, either to its osseous portion or the dura. Due to this peculiar feature, mandibular sarcomas are characterized by a better local control and a higher DFS and OS than the facial bones and skull base mesenchymal tumors [71].

In particular, when dealing with malignancies of the upper jaw, new technologies allowing careful three-dimensional tumor resection planning are helpful. Specific software that elaborates

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radiological Digital Imaging and COmmunications in Medicine (DICOM) images allows tailored surgical cutting guides to help precise excision of the tumor and high-quality simultaneous reconstruction, equally computer planned and guide-aided [72, 73].

Similarly, optimal margin control can be achieved also using intraoperative image-guided navigation systems that allow the comparison of the anatomical features with the available radiographic reconstructions, with a considerable learning curve [74].

On the other hand, while lower jaw resections are considered technically easier than upper jaw resection, due to more restricted growing patterns of the tumor and the relative lack of other fundamental surrounding structures, mandibular reconstruction is a major challenge for the surgeon. When dealing with defects following extensive mandibular resection, it is mandatory to evaluate which components of the hard and soft tissue are missing in order to select the best reconstruction method (from simple rigid internal fixation to microvascular free tissue transfer). It is also crucial to grant an adequate bone vertical height and to contour clearly the margins of the alveolar bone, in order to achieve both an aesthetically appealing result and to restore mastication to the patient [75, 76].

Furthermore, correctly designing the reconstruction and adequately reproducing the mandibular contour and the consequent occlusion allow for safe and correct implant placement, which restores the functions under a gnatologic and logopedic point of view [66].

While bony tissue reconstruction may pose the most challenging procedural issues, it has to be noted that soft tissue defect repair has a prominent role in preserving the patient's aesthetics. Healthy transposed soft tissue with an adequate height can adequately restore the facial contour, providing correct coverage of the underlying framework reconstruction [64, 76].

On the other hand, inadequately transposed soft tissues may produce poor results, requiring further ancillary procedure to replace the defect [77].

The use of neoadjuvant RTx in cervicofacial osteosarcoma, though not advised, has not been fully abandoned. Therefore, surgery may also follow RTx, which is a recognized major cause of increased surgical complications and free flap reconstruction failure, even with modern stereotactic protocols [78].

Such risk tends to increase proportionally to the RTx dose, since RTx induces definite changes in tissues (inflammation followed by fibrosis and a prothrombotic state with reduced vascular supply) which, in turn, lead to reduced wound healing and increased scar tissue formation [79].

In these patients, surgery can be performed, but both the surgeon and the patient must be aware of the higher complication rate and the postoperative management must be extremely careful. In these regards, it must be noted that the use of microvascular flap offers the best chances of a successful reconstruction, since the harvested tissue bears no microvessel damage due to radiation and is featured by a better overall vitality, given the appropriate blood supply through the anastomoses.

When dealing with head and neck malignancies, it comes naturally to evaluate a possible prognostic/therapeutic role for functional or selective neck dissection [80].

Although there is no general consensus, nodal localization should be treated surgically and should be considered adverse features when evaluating adjuvant treatments. Conversely (this is the major difference when compared to other common malignancies of the head and neck), prophylactic neck dissection is not advised also for high grade or large osteosarcomas of the head and neck region. Although more research would be advisable in these regards, it should be noted that the only, albeit old, data available report that prophylactic nodal dissection has a detrimental effect on patients' OS [81].

### 5.2. Medical treatment

The role of surgery in the treatment of jaw osteosarcoma is unquestioned [10].

The manuscript by Bertoni et al. [15] reported the Istituto Rizzoli-Beretta experience with JOS. They treated 26 of 28 patients with surgery and two patients with RTx. Adjuvant treatment was offered only to three patients (RTx in two cases and CTx in one): the 5-year OS rate for the whole group was disappointing (23%), as was the recurrence rate (85.7%). Such poor results are likely due to inadequate surgery (50% positive margins) and to the inefficiency of surgery as a single treatment [15].

While the use of preoperative and adjuvant CTx has become the standard of care in long bone osteosarcomas, its role in JOS is still controversial [11, 82, 83].

Adding CTx or RTx to surgery has demonstrated improved survival in locoregionally advanced head and neck cancer. The aim of chemotherapy is to reduce tumor size ameliorating surgical outcome, improve local control and reduce distant metastases. RTx is usually employed in the adjuvant setting and has the fundamental role of decreasing locoregional relapse.

The role of RTx in the multimodal treatment has been studied by Guadagnolo et al. [12]., who evaluated the role of RTx in 119 patients affected by JOS. While 92 patients underwent surgery alone, in 27 cases, surgery was followed by radiotherapy. Stratified analysis by resection margin status demonstrated that the combined use of surgery and radiotherapy was superior to surgery alone and could improve OS (80 vs. 31%) and DFS (80 vs. 35%) in patients with positive or uncertain margins. This high-risk group is inclined to get the best results, while no advantage is expected for patients with negative margins.

Two small retrospective studies on osteosarcoma of the jaws from Link et al. [82] and Doval et al. [84] using different CTx protocols in addition to surgery were the first to demonstrate that CTx could favorably impact on survival, though at a small rate.

The role of CTx (and RTx) has been further addressed in a systematic review on 201 patients from 20 uncontrolled series [14]. Various CTx regimens were given to 60 patients prior to (neo-adjuvant, 18 patients) or after surgery (adjuvant, 42 patients), performed in 180 patients. Surgical resection was complete in 105 cases (58.3%). RTx was used in 69 patients. The 5-year OS and Progression-Free Survival (PFS) in this group of patients undergoing multimodal therapy (surgery and neo-adjuvant and/or adjuvant Chemotherapy (CHT)) were 80 and 75%, respectively. The 5-year OS and DFS in those patients subjected to radical surgery alone were 40 and 33%, respectively. From this review, it was clearly evident that CTx significantly improved survival when combined with radical surgery, while the effect of RTx was insignificant [15].

http://dx.doi.org/10.5772/67564

The analysis of a small series of patients suggested the efficacy of multimodal treatment combining neo-adjuvant CTx, surgery and adjuvant CTx with excellent results in terms of 5-year OS and PFS [22].

A subsequent analysis on patients treated before and after 1991 demonstrated that the 5-year OS was 52% in the former group and 77% in the latter [85], reflecting earlier diagnosis and more aggressive treatment, namely the adoption of neoadjuvant CTx and of better reconstructive options.

According to Ferrari et al. [60], a multimodal approach consisting of radical surgery and CTx, with or without RTx, favorably compares with previous reports, achieving 5-year OS and DFS rates of 77 and 73%, respectively. In line with retrospective reviews stressing the prognostic importance of CTx-induced necrosis for local control [11, 25] also in this study, the rate of necrosis was a statistically significant factor, with poor prognosis correlating with ≤50% necrosis. These data confirm that JOS treated with perioperative CTx and radical surgery maximizes DFS and OS. CTx-related toxicity remains an issue that both oncologists and patients have to deal with. Adjuvant RTx can be useful in selected cases but the most relevant results are clearly related to the completeness of surgery.

Although multimodal treatment can improve clinical outcomes, what could be the best treatment for small, easily operable osteosarcomas remains to be assessed. It is likely that small low-grade lesions (T1) can be definitely eradicated by adequate surgery with no need for neoadjuvant or adjuvant therapy.

We do not think that we ought to discourage research, but it is reasonable to believe that controlled prospective and randomized trials on this argument are unlikely to be performed.

## 6. Conclusion

Through the years, the survival of patients with JOS has greatly improved, due to an aggressive systemic approach and to the refined surgical and reconstructive techniques. Today, we can reasonably hope to cure the majority of patients affected by JOS. However, opportunities for clinical and biological research remain. Our knowledge of the pathways involved in sarcomagenesis is lacking, and new insights are eagerly awaited in the perspective of developing an effective target therapy to combine with surgery.

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