



Multidisciplinary approach to osteosarcoma

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Osteosarcoma is a malignant bone tumor composed of mesenchymal cells producing osteoid and immature bone. Osteosarcoma is the most frequent primary malignant bone tumor, if we excluded myeloma, a haematologic disease.

The incidence of osteosarcoma is 2–3/million/year, but is higher in adolescence, in which the annual incidence peaks at 8–11/million/year at 15–19 years of age.

Local pain, followed by localized swelling and limitation of joint movement, are the typical signs and symptoms. Correct diagnosis can be achieved through a correct approach to the disease and the combination of clinical and radiographic aspects. The final step to confirm the diagnosis is the biopsy.

Computer Tomography of the chest and Positron-Emission Tomography are mandatory to complete the staging, which is performed according the Musculoskeletal Tumor Society staging system.

A multidisciplinary approach is needed both to get to a correct diagnosis (orthopaedic surgeon, radiologist and histopathologist) and to perform definitive treatment. Multidisciplinary approach should be performed in reference centers able to provide access to the full spectrum of care and where orthopaedic surgeon, oncologist, histopathologist, radiologist and radiotherapist can cooperate.

The management of osteosarcoma is based primarily on neo-adjuvant and adjuvant chemotherapy and surgical resection; radiotherapy is not effective as osteosarcomas are relatively radioresistant.

Prognostic factors include metastases at presentation, histologic response to induction chemotherapy, the site of the primary tumor (with axial lesions having

an inferior outcome), serum lactate dehydrogenase and alkaline phosphatase levels.

Keywords : multidisciplinary approach ; osteosarcoma ; treatment ; chemotherapy ; primary bone tumor.

CLASSIFICATION AND EPIDEMIOLOGY

Osteosarcoma (OS) is a metaphyseal malignant bone tumor composed of mesenchymal cells producing osteoid and immature bone (8). More rarely OS may arise in the soft tissues. OS is the most frequent primary malignant bone tumor, if we excluded myeloma, a haematologic disease.

There are several varieties of OS which can be divided into two groups: high-grade and low-grade. The last one are very different in their clinical, pathologic and therapeutic-prognostic features and

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are classified as separate entities (periosteal OS, parosteal OS, low-grade central OS). High grade OS can be divided into different subgroups: classic OS, teleangiectatic OS, OS of jaw bones, secondary OS, small cell OS, high grade OS of the surface, multicentric OS, intracortical OS (8).

This paper refers only to the classic high grade primary OS of bone, which represents about 90% of all cases of OS.

The incidence of OS is 2–3/million/year, but is higher in adolescence, in which the annual incidence peaks at 8–11/million/year at 15–19 years of age (45).

Other cases of OS can be observed during advanced age but they are usually secondary to other conditions, such as Paget's disease, irradiated bone, chronic osteomyelitis, bone infarct and dedifferentiated chondrosarcoma. Very rare cases are reported to be related to benign conditions, such as Giant Cell Tumors, chondromas and non-ossifying fibromas (4).

The more frequent areas are distal femur, proximal tibia, proximal femur, proximal humerus and diaphysis of long bones. However, OS can also oc-

cur in the axial skeleton, most commonly in the pelvis (10,17).

Diagnosis

Local pain, followed by localized swelling and limitation of joint movement, are the typical signs and symptoms of osteosarcoma. In rare cases, particularly in patients with osteolytic tumors, a pathological fracture can be the first sign of disease (45).

The correct diagnosis of OS can be achieved through a correct approach to the disease and the combination of clinical and radiographic aspects. The final step to confirm the hypothesis is the biopsy. The most important clinical aspects are the age of the patient and the site of the tumor.

Plain radiography is helpful to describe osseous changes: OS can present with osteoblastic, osteolytic or mixed appearance (Fig 1). They often have a soft tissue component in which patchy calcifications resulting from new bone formation or spiculae may be observed. A triangular area of periosteal calcification in the border region of tumor and healthy tissue is known as a Codman triangle, which is consid-

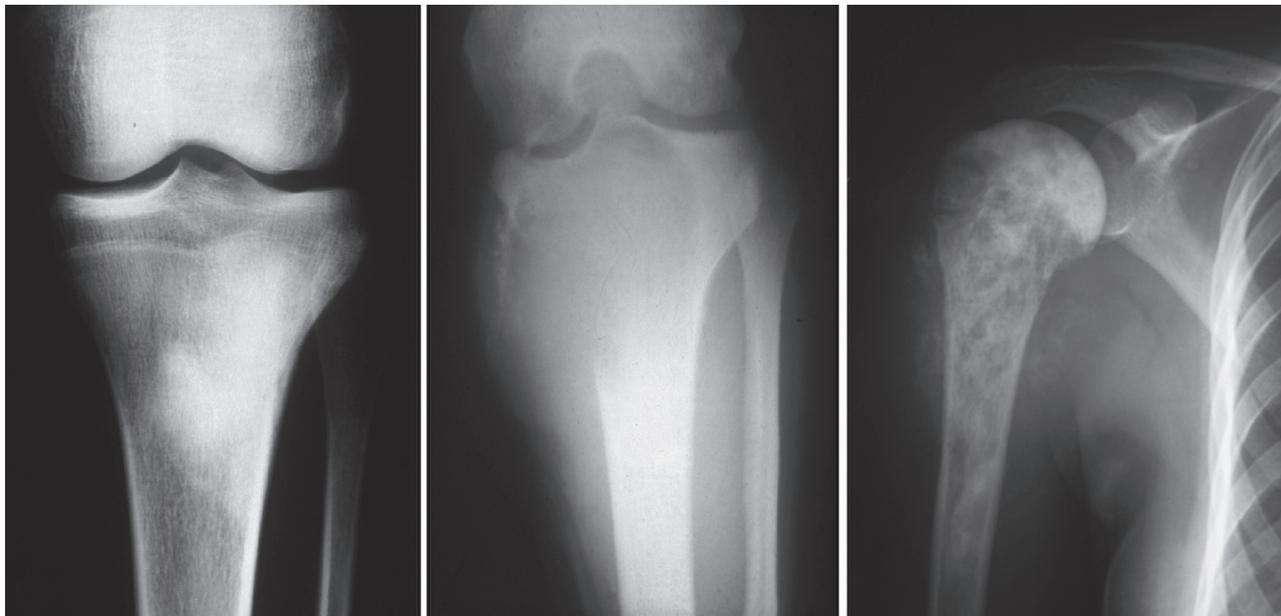


Fig. 1. — On the left: osteoblastic OS of the proximal tibia. In the center: osteolytic OS of the proximal tibia. On the right: osteoblastic-osteolytic OS of the proximal humerus.



Fig. 2. — Distal femur OS. Arrow: skip lesion.

ered typical for OS. Magnetic Resonance Imaging (MRI) is the best modality to assess the soft tissue component, its relationship to surrounding tissues, vessels and nerves and its intramedullary extension, such as skip lesions (45) (Fig. 2).

The final and necessary step to diagnosis is the biopsy. Biopsy material should be obtained by the use of either a large core tissue biopsy or by an open biopsy. The use of cytologic or fine-needle aspiration should be avoided as it frequently leads to under-diagnosis or incorrect diagnosis. It's important to place the biopsy tract in an area where it can be totally excised, if the patient will be successively treated by limb salvage (43).

The true-cut needle biopsy with large core is the most frequent and preferred type of diagnostic method and it can be performed free-hand or computer-tomography (CT)-guided, such as in the pelvis and column. When biopsy material is insufficient incisional biopsy should be performed.

CT of the lungs and Positron-Emission Tomography (PET) are mandatory to complete the staging.

So, a multidisciplinary approach is needed to get to a correct diagnosis, with cooperation between orthopaedic surgeon, radiologist and histopathologist.

The differential diagnosis includes infections as well as other tumors, such as aneurysmal bone cyst, Ewing's sarcoma and chondrosarcoma.

Staging

OS is staged according the Musculoskeletal Tumor Society staging system (16), which distinguishes between two grades of malignancy (low versus high), intra- (A) and extracompartmental (B) extension. This system categorizes localized malignant bone tumors by grade and by the local anatomic extent. The compartmental status is determined by whether or not the tumor extends through the cortex.

At presentation 80% of OS are stage II-B; only 5% are stage II-A, because most high-grade OS break through the cortex early in their natural history. About 15% of OS are stage III (metastatic disease) (30). Virtually all patients are presumed to have subclinical microscopic lung metastases (34).

Treatment : the multidisciplinary approach

A multidisciplinary approach is needed in the treatment of patients with OS and should be performed in reference centers able to provide access to the full spectrum of care and where orthopaedic surgeon, oncologist, histopathologist, radiologist and radiotherapist can cooperate.

The management of OS is based primarily on neo-adjuvant chemotherapy, surgical resection and adjuvant chemotherapy; radiotherapy is not effective as osteosarcomas are relatively radioresistant. Since 1970, when OS was treated with amputation and/or radiotherapy, more than 80% of patients developed metastatic disease following therapy (44). Advances in chemotherapeutic regimens, surgical techniques and radiologic staging studies have enabled 90% to 95% of patients to be treated with limb-sparing resection and reconstruction. Nowa-

days, survival rates at 5 years ranging from 60% to 70% for localized OS of the extremities (48).

Chemotherapy

The concept of neoadjuvant chemotherapy was introduced by Rosen in 1976, when he argued that chemotherapy administration prior to definitive surgery could offer the opportunity to develop a custom-made prostheses for limb-salvage procedures and the theoretical advantage of early treatment of micrometastases while facilitating the surgical procedure (47). It also provided the opportunity to examine the histological response of the tumor to chemotherapy and assess its effectiveness. A strong correlation between the degree of necrosis (28) and subsequent disease-free survival was observed. Then, several studies proved the efficacy of chemotherapy in the treatment of OS (34,14,15,46).

The identification of the prognostic value of the degree of necrosis following chemotherapy led to the suggestion that chemotherapy could be modified for patients with less necrosis (currently, poor responders are those patients with less than 90% of necrosis) in an attempt to increase the probability of disease-free survival. Investigators at Memorial Sloan-Kettering Cancer Centre reported an improved outcome for patients with poor histological responses following a change in postoperative therapy (46).

Nowadays, the most active agents for OS include cisplatin, doxorubicin, ifosfamide and high-dose methotrexate. Etoposide has little activity in OS when used as single agent and its use has been proposed in combination with ifosfamide. The standard postoperative-chemotherapy for poor-responders is based on the combination of ifosfamide and etoposide, useful also in metastatic patients.

Recently, the Children's Oncology Group (COG), Cooperative Osteosarcoma Study Group (COSS), European Osteosarcoma Intergroup (EOI) and Scandinavian Sarcoma Group (SSG) designed a study (EURAMOS) to determine whether pegylated interferon (IFN- α -2b) could improve the outcome in good responders. The first results show that in good responders methotrexate, adriamycin and cisplatin (MAP) plus IFN- α -2b is not statistically dif-

ferent from MAP alone. A considerable proportion of patients stopped IFN- α -2b due to toxicity (6, 38).

Unfortunately, for the treatment of advanced disease there are no specific protocols; so these patients underwent the same chemotherapy of localized disease with poor results (1,20).

Besides, the use of chemotherapy is associated with acute and long-term toxicities, such as hearing loss (7) and hypomagnesemia (26) associated to cisplatin, anthracycline-induced cardiomyopathy (32), nephropathy due to methotrexate, sterility and leukemia.

Surgery

Surgical treatment of localized OS is the main treatment modality and follows neoadjuvant chemotherapy and precedes post-operative treatment. When possible, tumor excision should be performed with wide or radical margins. Nowadays, the use of neoadjuvant chemotherapy has enabled surgeons to perform limb-salvage surgeries in the most of cases (39).

After tumor excision, the type of reconstruction depends on the site of the tumor and the age of the patient.

Generally, in immature patients, almost one of the growth centers is compromised after tumor excision. In order to accommodate skeletal growth, different devices can be used, such as expandable prosthesis (Fig. 3) and limb lengthening via distraction osteogenesis. When the tumor is diaphyseal, allograft intercalary reconstruction is preferred (Fig. 4). Vascularized fibula is an important option in diaphyseal locations and as salvage technique in failure of previous limb reconstructions (9) but has donor site morbidity.

Structural allografts have no donor site morbidity. Their advantage is that they represent a biologic solution and, if they heal and do not fracture, may last the lifetime. The major problems are nonunions, infections and fractures.

Infections can occur in 10-15% of allograft reconstructions (9) and nonunions at the osteosynthesis can occur in another 10-25% (21). Both these complications are more likely in patients receiving chemotherapy. Augmentation of the allograft with



Fig. 3. — Distal femoral reconstruction with expandable prostheses in immature patient.



Fig. 4. — Intercalary allograft reconstruction after diaphyseal femoral resection for OS.

vascularized fibula may facilitate osseous integration of the allograft and prevent nonunions and fractures (37).

In relatively young-adult patients, allograft-prosthetic composites (APC) (27) can be an optimal option of reconstruction in proximal femur, proximal tibia and proximal humerus. Their advantage is the hybridization of a more conventional arthroplasty with potential incorporation of the allograft for future bone stock (Fig. 5).

In mature patients, metallic modular endoprostheses provide an immediate stable solution (Fig. 6). Among complications, infections are the most likely, with rates ranging from 0% to 35% (22,40,36). The durability of the prostheses is influenced by many factors, such as the site of the tumor, the type of the prostheses and weight and style of life of patients. Prosthetic reconstructions of the proximal humerus tend to be more durable since they are not subjected to weight-bearing stresses.

Saddle prostheses, allograft, APC and endoprostheses represent different options of reconstructions when the tumor is localized in the pelvis. All these techniques are characterized by several complications, such as infections, fracture and aseptic loosening. Nowadays, saddle prostheses are used only as salvage technique for failure of previous reconstructions. Allograft reconstructions represent a suitable solution for periacetabular lesion (3,12,13,23) and are characterized by low rate of complications, but should be performed only in reference centers.

Radiotherapy

Since OS has low sensibility to radiation therapy, radiotherapy is generally used only to treat lesions located in inaccessible sites or in inoperable patients. Preoperative radiotherapy could be given before the surgery to increase the success rates of limb-amputation techniques and reduce the risk of recurrence of the tumor. High-dose photon irradiation (50-70 Gray) can be used in combination with aggressive chemotherapy when tumors are located in inaccessible sites such as pelvic region, vertebral column and base of the skull. This irradiation is also useful in patients who do not consent to surgery (11).

The use of targeted radiotherapy with Samarium-153-ethylendiamine tetramethylene phosphonate may



Fig. 5. — Reconstruction of the proximal humerus with APC.



Fig. 6. — Reconstruction of the distal femur with modular prostheses.

also be considered in selected situations, although the role of this treatment modality is not well defined and its definition would require further evaluation in controlled clinical trials (19,20).

Prognostic factors

The most important prognostic factor at diagnosis is the presence of clinically detectable metastases, which confers an unfavorable prognosis (5). The histologic response to induction chemotherapy is the second prognostic factor but cannot be assessed at the time of the diagnosis. Histologic response can be assessed on the specimen: tumor necrosis

of >90% following neoadjuvant chemotherapy has been correlated with improved survival rates and is scored according Huvos' classification (28).

The 5-year survival rates for patients with >90% tumor necrosis are reported

to be >61%, but drop to 37% to 52% in patients with a poor response (necrosis <90%).

Despite current surgical and chemotherapeutic treatment regimens, 30% to 40% of osteosarcoma patients experience relapses within 3 years of treatment (35,41). Pulmonary recurrence is most commonly secondary to micrometastatic disease (41). Patients should be counseled on the poor prognosis associated with relapse because the long-term survival rate is <20% (2,18,31).

Regardless of the poor prognosis, patients should be offered repeated tumor excision because some studies have demonstrated improved survival rates (25). The role of second-line chemotherapy remains controversial because no standard chemotherapy regimen exists for recurrence.

The third important prognostic factor is represented by the site of the primary tumor, with axial lesions having an inferior outcome (42). Also serum lactate dehydrogenase (LDH) and alkaline phosphatase levels correlate with outcome (33).

Different clinical studies have already underlined the natural history of drug resistance of OS, which occurs in 35-45% of patients. Therefore, the identification of drug resistance-related markers as prognostic factors and new potential targets is highly recommended (24).

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