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REVIEW ARTICLE

Treatment of Osteosarcoma. A Review

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Abstract
An update on the conventional treatment of osteosarcoma, excluding secondary forms due to malignancies by other diseases, as well as the parosteal-juxtacortical forms. The overall survival is 73%, although the protocol is still open. The toxicity and changes established in the forms of administering the drugs to decrease the secondary effects in the short and long term are assessed.

PALABRAS CLAVE
Osteosarcoma;
Tumor óseo;
Quimioterapia;
Cirugía de rescate

Tratamiento del osteosarcoma. Revisión

Resumen
Se presenta una actualización del tratamiento del osteosarcoma convencional, con exclusión de las formas secundarias por malignización de otras patologías, así como las formas de osteosarcoma parostal-yuxtacortical. La supervivencia global es del 73%, aunque el protocolo sigue abierto y se evalúa la toxicidad y se plantean cambios en la forma de administrar las drogas para disminuir los efectos secundarios a corto y largo plazo.

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Introduction

Sarcomas are malignant tumours of the musculoskeletal system and connective tissue, as well as the peripheral nervous system. The characteristics that are common to all sarcomas are there rarity in comparison with carcinomas, whose highest incidence is during childhood or infancy and that affect any organ structure, with the extremities and retroperitoneum being the most commonly affected places. In the skeleton, sarcomas can appear derived from all cell lines. Thus, round cell tumours can be found, such as bone lymphomas and Ewing's sarcoma, or tumours that arise from notochordal remnants, such as chordomas. Nevertheless, the overwhelming majority of primary tumours of the skeleton depend on three varieties of spindle cells that comprise the largest portion of their volume: fibrosarcomas derive from the fibrous matrix, chondrosarcomas from cartilage, and osteosarcomas (OS) arise from bone.

OS or bone sarcomas (BS) are the most common sarcomas of the skeleton, at all ages and their fundamental characteristic is that they are not located in the bone, but develop from the stem cells in charge of generating normal bone. The histological reference of this origin, on which the certain diagnosis of OS depends, is the appearance of *de novo* bone tissue, at the core of the tumour itself. This can take the form of more or less disorganized bone, in various phases of maturity or, more commonly, of osteoid [tissue]. It is even possible that these stem cells are located outside of the skeleton on occasion, the so-called extraskeletal OS, in the same way that occurs with supernumerary breast tissue or with extragonadal germinal tissue. If any of these cells were to follow a pathway of malignant transformation, it would give rise to a sarcoma, that would be a soft tissue sarcome based on its anatomy and OS according to its histology.

The vast majority of BS are sporadic and only a tiny percentage [of the patients] have a history that includes predisposing factors, such as radiation, Paget's disease, or hereditary disorders. BS are uncommon in adults and much more frequent in younger-aged individuals. Thus, it ranks after twentieth in the classification by frequency of all cancers in adults, but is less than comes in within the top five if we consider the age group under-20 years old. Its incidence curve reflects a sharp peak in individuals aged 11-20 years and another much smaller one among peoples with ages between 60-80 years. This peak coincides precisely with the acceleration of growth, to the point that precocious development in girls faithfully reflects an earlier increase in the incidence of BS.

Childhood BS are closely linked to growth and are probably related to mitotic errors in the genes involved in controlling growth, perhaps in the stem cells that cause bone lengthening and maturity. Thus, tumours in children concentrate in the para-articular areas of long bones, whereas in the adult, totally unrelated to growth, they appear more often in the axial skeleton.

The metaphyseal areas of the long bones are the most commonly affected. In contrast, while BS in children are almost always of the classical type, in the adult, they can also be atypical, for instance parosteals, mandibular, or extraskeletal. It is hard to think that, even though they have a shared histology and denomination, both entities should be considered the same disease from a biological point of view. And yet, much of the knowledge we use to establish a prognosis and to treat BS in adults have been taken directly from the body of research evidence from the study of pediatric BS, as there is a tremendous paucity of studies specifically designed for adult-aged subjects.

Clinical Manifestation

The symptoms of OS tend to be insidious and by and large, the definitive diagnosis is preceeded by a long history of consultations and failed treatment attempts. Pain is the most common presenting complaint, sometimes related to some kind of recent trauma. The absence of specific early signs, the low suspicion of tumours in children, and the extremely high frequency of similar benign painful syndromes in the clinics of pediatricians, primary care physicians, and regular traumatologists come together and make it possible for sarcoma to remain camouflaged for weeks or months after diagnoses such as growing pains, tendinitis, or muscle fatigue.

In the case of the atypical, indolent varieties in the adult, it is not unusual for it to take years to reach the diagnosis. Most of the times, the suspicion of sarcoma arises when a tumour appears on an MRI performed in the course of investigating pain. OS of the extremities cause palpable tumours sooner, which makes for an earlier diagnosis in comparison with centrally located OS.

Laboratory values are generally normal with the exception of elevated alkaline phosphatase, LDH, or rate of red blood cell sedimentation. Only the most outlying LDH values are related with an unfavourable prognosis.

BS in adults have a worse prognosis than they do in children. The Mayo Clinic registry[1] reveals a 70% rate of metastasis and the same percentage of mortality. One in three tumours was located in the axial skeleton and one in five tumours was diagnosed as a stage IV at the outset. Pathological fracture and local relapse were two circumstances that pointed toward a poor prognosis. All patients with local relapse and all who presented fractures and in whome immediate amputation was not performed ended up developing metastases and died. The data from the Memorial Sloan Kettering Cancer Center,[2] despite being more up-to-date, are no more encouraging; 66% of all diagnosted patients passed away. Nevertheless, those who had received poly-chemotherapy, especially high-dose methotrexate, presented more optimistic relapse and survival figures. It is possible that the prognosis for OS in adults is not essentially any worse, case by case, than it is in children or adolescents, but rather that the overall statistics reflect a higher proportion of axial sarcomas that are more difficult to diagnose and prone to surgical treatment that is less satisfactory.

Diagnosis

The diagnosis of OS is founded on a protocol based on imagning studies and laboratory tests that provide a

diagnostic orientation and are confirmed by biopsy and the pathology study of the tumour tissue. After clinical symptomatology that suggests the existence of a bone growth, we initiate an imaging study that will consist of an x-ray of the area affected to evaluate the macroscopic extension and the bone affected, its relation with and the involvement of near-by structures and the existence, on occasion, of a pathological fracture.[3] With this first orientation, we move on to a CT CT scan or MRI study. Each of these techniques has its indications. The CT scan is a fact and simple technique, whereas the MRI requires total immobilization for a long period of time and, in the case of children, requires their collaboration and at times, it is necessary to sedate or anesthetize them. In general, the MRI is the technique of choice, given that it provides better information as to the overall extension of the tumour, the infiltration of neighbouring structures, the vascular-nerve bundle, etc.; all of which are data of interest for the subsequent planning of surgical treatment. Moreover, it quantifies the size of the tumour, which constitutes an important prognostic datum.[4] In the initial study, we mustn't forget to perform a CT scan of the lungs to rule out the existence of metastasic dissemination at this site; the most common one.

The bone gammagraphy with Tc^{99} provides fixation of the radioisotope in the primary tumour and provides information about the involvement of other bones. It also serves to detect local or metastatic relapses.

The option of performing a PET is gradually gaining ground, since it is a highly profitable technique for gaining information about primary lesions and also to detect multiple lesions in other bones, not always evaluated by other studies, as well as to detect pulmonary metastasis. A PET performed at the onset of illness serves as a baseline for subsequent control of the evolution [of the lesion(s)] and constitutes a technique capable of detecting tumour foci that are not evaluable by means of other types of examinations.[5,6]

After the imaging studies, a biopsy of the lesion will be needed. Osteogenic sarcomas are classified by their origin as being intramedular or juxtacortical. From a histological point of view, intramedular OS present variants based on the predominant matrix or stroma cell type present in the lesion. The most common variant is the osteoblastic type comprised of osteoid material-producing, spindle-shaped malignant cells. The chondroblastic and fibroblastic forms account for one fourth of each of form. On the histology study, the telangiectasic variant is characterized by the presence of blood and tumour cell filled spaces with little stroma and is often associated with pathological fractures because of the highly fragile nature of the tissue. The small, round cell variant with cellularity similar to that of Ewing's sarcoma at times will call for specific immunohistochemical or genetic marker studies in order to establish its diagnosis.

Juxtacortical OS originate on the internal surface of the bone, distinguishing three subgroups: paraosteal, periosteal, and high grade. The paraosteal group is the most common one, with fibroblastic stroma and foci of cartilage. The periosteal group grows on the surface of the diaphysis, generally the tibia or the femur. The high grade superficial group tends to appear in adults and requires aggressive treatment, as do the intramedular type.

Imaging studies locate the lesion; the biopsy names the lesion, and with these data the tumour is defined so that the most suitable treatment can later be applied. In line with the now well-known Enneking classification,[7] OS are divided into 5 stages. Treatment will distinguish between high grade, low grade, and metastatic OS, with different degrees of aggressiveness for each.

Biopsy in Osteosarcoma

Before considering biopsy, the entire iconographic study of the lesion to be biopsied should be available to aid in located the site of biopsy and to avoid local, secondary alterations and to orient the session with specialists in diagnostic imaging should there be any doubt.

The ideal biopsy technique in OS is by puncture using a bone trephine under radioscpic guidance. Bearing in mind the most common locations of this neoplasm, the metaphysis of the distal femur or proximal tibia and the proximal metaphysis of the humerus, this technique can be applied in most cases; the need to perform an open biopsy is rare. When there is a soft tissue mass, a tru-cut biopsy will suffice, although ideally, the biopsy will include a sample of said mass together with the bone.

The determining factors that an open biopsy poses for the subsequent surgery are very important, as it will be necessary to split the resulting scar together with the full resection of the tumour. Shoul dit be necessary, the open biopsy should be performed by the same surgical team that will be treating the OS. In addition, aggressive biopsies must be avoided to as to prevent secondary pathological fractures.

A poorly performed open biopsy with a wide window using an osteotome and causing a pathological fracture can end up in amputation or local dissemination, making it impossible to salvage the limb surgically. The biopsy should be contemplated as a surgery and be carried out under the strictest conditions of sterility; infection of the course of the biopsy can condition the entire posterior course.

Although it has been mentioned that the incision of a biopsy should be made by the specialized team, the principles for making incisions must be remembered, following the path of the surgery to be scheduled; they will be longitudinal with respect to the axis of the extremity, avoiding transversal incisions. Likewise, plane disections should be avoided; hemostasis must be assured so as to avoid local dissemination of the hematoma with tumour cells, and Penrose drains must be avoided given that because they discharge out through the biopsy wound, will cause a pathway of exophytic growth of the tumour. Should it be necessary, the drainage should be by aspiration and should drain out through one of the incision poles. Finally, strict closure must be carried out plane-by-plane and sutured with non-reabsorbible material.

The obsession and aqccuracy of "taking a large sample" is the consequence of a poor relationship with radiodiagnostic and pathology teams. This attitude can guarantee the diagnosis, but at the price of severely conditioning treatment and prognosis.[8]

Chemotherapy

Classical OS is the oncologic paradigm of micrometastasic disease, that must be considered disseminated in any of its stages and that, as a result, will always require systematic treatment. The micrometastasis hypothesis contributed to the incorporation of chemotherapy to the multidisciplinary treatment of OS.

Many years after the use of chemotherapy became a daily practice, immunogenetic detection techniques revealed that the existence of micrometastases in blood and bone marrow was a fact that determined patient outcomes.[9] Until the advent of efficacious chemotherapy, a number of surgical stategies were used, albeit none of them were capable of lowering mortality to less than 80% The optimal poly-chemotherapeutic treatments can turn two thirds of the patients into survivors.

Chemotherapy is capable of curing disseminated OS when the tumour volume is still microscopic.[10,11] Although the use of chemotherapy as a complement to surgery in all patients diagnosed with OS, whether pediatric or adult patients, is a universally accepted fact and has been for many years now, the ideal composition of treatment and the best timing for its application continue to be subject to debate. The controversy is greater when dealing with adults.

The best outcomes in children were obtained by adding high doses of methotrexate to cisplatin- and adriamycin-based regimens. This type of regimen was soon administered prior to surgery, instead of postoperatively. Initially, this strategy was practical, dictated by the need to control the growth of the tumour while the metal endoprosthesis was being manufactured,[12] however, soon that reducing the bulk of the tumour was useful so that conservative, less mutilating surgeries could be performed. The doubt remained as to whether the delay in local treatment compromised the probability of a cure and multicentre clinical trials have demonstrated that the probabilities of surviving are similar, regardless of whether the chemotherapy is used prior to or after surgery.

In addition to making survival possible and to improving local control, preoperative chemotherapy indicatedsthe sensitivity to treatment in each patient, in the form of the degree of necrosis observed in the surgical specimen. One of the most appealing directions has been that of attempting to customize treatment for each individual patient based on his/ her response to neoadyuvante treatment.[13]

The degree of necrosis is a first order prognostic factor. It has been seen that in those patients who present a complete or almost complete pathological response, although poorly correlated with clinical or radiographic response, had a 5-year supervival rate of more than 80%, whereas those subjects who did not present histological changes or, even, those who had remarkable degrees of necrosis although less than 90%, had a 5-year mortality rate of more than 60%or 70% It was thought that patients who failed to respond to treatment might improve their prognosis if they were treated after surgery using active agents with a mechanism of action that was so different as to prevent cross-resistance. That was the way it was, at least at the beginning, and treatment switching in resistant subjects improved their prognosis to the point that it approached that of the group of responders.[14] This is based on Rosen's T10 protocol, which has been the compass that has guided the oncological treatment of sarcomas for many years. Nevertheless, as time has gone by, the effect has been disappearing and the supervival curve of non-responders has gradually separated from that of those who attain excellent degrees of necrosis following initial treatment.[15]

On the other hand, other cooperative groups have been incapable of reproducing the initial outcomes attained at the Memorial Sloan-Kettering Cancer Center of New York, at least with the same degree of efficacy. It would therefore appear that the strategy of switching chemotherapies without cross resistance based on necrosis is incapable of saving more lives over the long term, although it does prolong the disease-free interval and stratefies patient prognosis much better.

The resoponse rate seen in metastatic patients using a new regime based on iphosphamide and etoposide (I/E)[16] has opened the way to the hope of improving the prognosis of non-responders by modulating treatment. One large international cooperative trial, pending final results, is exploring the addition of I/E to the postoperative phase in patients with low degrees of necrosis.

One pressing issue in the treatment of adults with OS has to do with the fact that practically all the seminal studies mentioned were conducted mostly or exclusively in children and adolescents, leave a large margin of doubt with respect to extrapolating their conclusions to patients over the age of 30. Thus, the Rosen's T10 protocol was tested in subjects under the age of 21 years; the high-dose methotrexate study excluded patients over the age of 15 years and has not demonstrated that it increases survival in the few and small trials dedicated to adults; the comparison of neoadyuvante chemotherapy with adyuvante chemotherapy was limited in its initial trial to patients under the age of 30 years and the on-going clinical trial with the I/E treatment scheme includes patients of up to 31 years old.

BS in the adult must be understood and its biology, prognostic factors, and the best adyuvante treatment must be determined. Clinical trials shouldn't exclude adults, but rather they should be stratified to allow their data to be analyzed, no matter how scant they are, without contaminating the data regarding children and adolescents. In the meantime, young adults (under the age of 50 or 60 years) should not be deprived of the benefits reserved to younger patients.

Surgical Treatment of Osteosarcoma

Without treatment, there is no possibility of curing OS. Although disseminated metastasic disease is the cause of death and chemotherapy has achieved a radical change in supervival figures, chemotherapy on its own cannot be maintained by itself, as it is incapable of eradicating the primary tumour. Therefore, the surgical treatment of conventional OS is intertwined with preoperative chemotherapy and postoperative chemotherapy.

The aim of the treatment sequence "preoperative chemotherapy and postoperative surgery-chemotherapy" seeks to control the microsopic disease not initially

detectable, reduce the tumour volume, necrotise the primary tumour and to make it possible to orient postoperative chemotherapy based on the rate of necrosis evaluated in the specimens derived from resection or amputation.

The surgery, following similar protocols in children and adults, is carried out approximately 15 weeks after initiating chemotherapy. This is an important advantage for the oncological surgeon in appropriately planning the type of intervention and reconstruction to be performed. In contrast, we have not observed significant decreases in tumour volume, as was initially claimed, with preoperative chemotherapy.

One disadvantage of preoperative chemotherapy is the risk of provoking a pathological fracture in lytic OS, as seen in telangiectasic OS that must be prevented by the zx descarga in tumours of the lower limb.

The main disadvantage of postoperative chemotherapy is the risk of infection of reconstructions, especially in the tibia, which often leads to its being delayed until 3 or 4 weeks after the intervention, if the local status of the surgical wound so indicates.

The clinical situation and the imaging studies in non-disseminated patients is the basis for deciding whether to perform a limb-salvaging surgery or to amputate. Coordination with the pathology and radiodaignostics services is essential when making this decision.

The limb can be saved when resection can be achieved with a 5-cm margin, at the medular level, if resection of the extra-osseous-soft tissue tumour makes acceptable functionality possible, and when the vascular-nerve packet of the extremity, after tumour resection, guarantees the subsequent viability of the limb. In the articular portion, the margin can be adjusted further by the barrier effect of the articular cartilage.[17] In selected cases, vascular segments are resected with a repair by-pass, although they must be evaluated on a case-by-case basis, both prior to and during surgery.

Reconstructions in oncological orthopaedic surgery are possible with massive structural homografts, customized megaprostheses, and modular tumour megaprostheses. The use of systems consisting of megaprostheses and homograft are the authors' preferred choice in treating young patients, while we reserve modular arthroplastis to middle-aged and elderly patients or when the resection limits cannot be determined precisely, allowing a modular system to adapt to the intraoperative circumstances and findings.[18,19]

Osteoarticular homografts in the area of the knee and in loading joints were abandoned in light of the ensuing complications, as well as because those that were used in the reconstruction of the proximal humerus presented high fracture rates in the grafts. In young patients, we prefer to used compound systems, and, in middle-aged patients, modular megaprotheses. By location, the reconstruction modalities in OS are the customized arthroplasty consisting of a structural homograft in young patients and modular artroplasties in middle-aged patients or in those in whom it is difficult to preoperatively evaluate the levels of resection (fig. 1) in the femur distal. In the proximal femur, we indicate arthroplasties with diaphyseal anchoring with homograft to insert the pelvic-trocanteric in young patients and the modular artroplasties in middle-aged individuals.

In the proximal tibia, customized megaprostheses with massive structural homograft are indicated for repair and bone reinsertion of the extensor apparatus (fig. 2), and in the proximal humerus, we advise a customized artroplasty

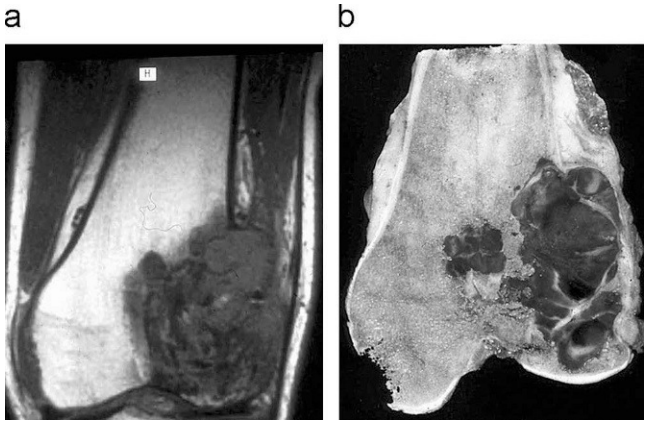

Figure 1 a) Radiographic appearance and b) macroscopic aspect of a femoral osteosarcoma resection specimen.

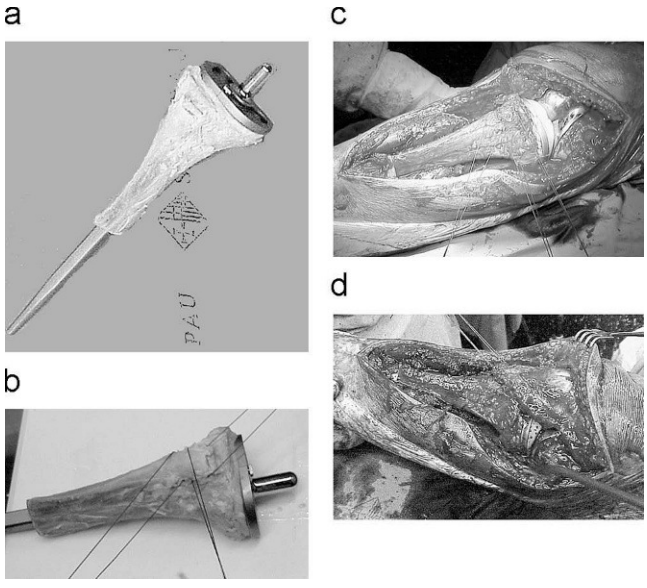

Figure 2 a) Combination of megaprosthesis with structural tibial homograft, b) anchoring of the patellar tendon, c) implantation, and d) reconstruction.

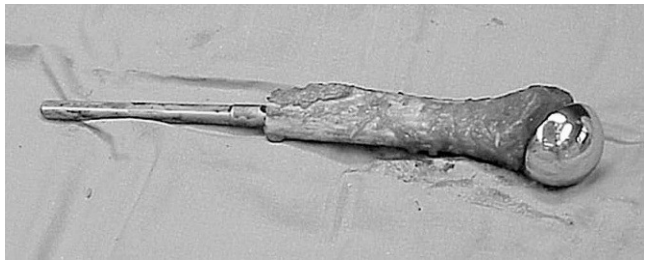

Figure 3 System comprised of a megaproisthesis and homograft for reconstruction of the proximal humerus and rotator cuff and capsule repair.

with a structural homograft that includes the donor capsule and rotator cuff (fig. 3). The remaining locations cannot be protocoloized because of their lower incidence and are planned specifically for each tumour. Complete reconstructions of the femur and humerus are exceptional in OS.

The proportion of limb salvage versus primary amputation in OS between the years 1983-1999 was 3:1 and local relapse rates after limb salvage of the same team during this time period were 15.3% in resections of the tibia, 10.3% in resections of the femur, and 5% in resections of the humerus.

The immediate postoperative complications associated with limb salvage surgery in OS are concentrated in the tibia and consist of infections, compartmental syndromes, ruptures, and disinsertions of the extensor apparatus; however, in most of the series, long- and mid-term complications are left out. In our experience, the complication rate was 11%, from 2-5 years after salvage surgery. These complications in 161 reconstructions consisted of material breakage, homograft fracture, pseudoarthrosis with clinical-mechanical translation, dislocations, and hematogenic infections. Long-term (more than 5 years), local complications should not be overlooked that, in our experience, occur in as many as 2.4%. Nor should mechanical complications be overlooked with reinterventions due to mechanical loosening that will inevitably happen in such a young surviving population who demand activity. These patients should therefore be advised of the causes of deterioration of the reconstructive assemblies, steering clear of claiming victory as too often occurs and fostering the performance of these surgeries by highly specialized teams.

Experience and results of the Spanish Society of Pediatric Oncology

For the Spanish Society of Pediatric Oncology (SEOP, for its Spanish acronym), OS is the most common bone neoplasm, located predominantly in the bones of the lower limbs in young patients. The historical prognosis has changed over the last three decades in response to the use of more effective chemotherapy that have lowered the incidence of metastasis and mortality. The international medical literature reports a 5-year supervival rate for patients diagnosed in the 1974-1994 time period of 63% and, at present, we are attempting to improve these figures while decreasing amputations and the short- and long-term sequelae. Very recent reviews of large cooperative groups have evaluated the importance of different prognostic factors, separating groups based on these criteria and, although survival expectations for localized OS have improved slightly, there is a 9%posibility of them debuting with metastases at the time of diagnosis.

1995 Protocol of the Spanish Society of Pediatric Oncology for the Treatment of Osteosarcomas

The SEOP drafted a first treatment protocol that was activated in 1995 and closed in 2001, the results of which are presented below.

The treatment regime consisted of using four basic drugs:

Iphosphamide (1,800 mg/ m^2 intravenous [IV], in 1 h, 5 days) (week 0, 5).

Adryamycin (25 mg/ m^2 IV, in 18h, 3 days) (weeks 0, 5 and 10).

Methotrexate (12 g/ m^2 IV, in 4h, 1 day) (weeks 3, 4, 8, 9, 13, 14).

Cisplatin (120 mg/ m^2, in 4h, 1 day) (weeks 10).

At week 15, surgery was peformed and postoperative chemotherapy consisted of:

Iphosphamide (1,800 mg/ m^2 IV, in 1h, 5 days) (weeks 17, 22, 23, 37).

Adryamycin (25 mg/ m^2 IV, in 18h, 3 days) (weeks 17, 22, 27).

Methotrexate (12 g/ m^2 IV, in 4h, 1 day) (weeks 20, 21, 25, 26, 30, 31, 35, 36, 40, 41).

Cisplatin (120 mg/ m^2, in 4h, 1 day) (weeks 27, 42).

In this protocol, a total of 136 patients were registered in 22 hospitals, of which 116 were analyzed, given that 20 were excluded due to protocol violations. There were 100 cases of localized OS and 16 cases of metastatic or multicéntrico OS (13.8%) (table).

Surgery was performed at the outset in two cases, given that the presented pathological fractures as their first symptom. Of the remaining patients, 16 (15%) required amputation and 94 underwent conservative surgery. Insofar as the histological response obtained by assess the degree of necrosis, a good response was obtained in 67% (>90% of necrosis) and in the remaining 33%, response was poor. Of the 100 patients with localized disease, 9 presented local relapse (table 2).

Table 1 Cases of the 1995 Spanish Society of Pediatric Oncology

Hospital	Patients
Sant Pau	17
Ramón y Cajal	17
Virgen del Rocío	15
La Paz	10
Valle d'Hebron	9
Niño Jesús	8
S. Joan de Déu	8
Central de Asturias	7
12 de Octubre	4
Virgen del Camino	3
La Fe	2
Cruces	2
Carlos Haya	2
Clínico de Valencia	2
Juan Canalejo	2
Basurto	2
Miguel Servet	2
Sabadell	1
Virgen de Arrixaca	1
Virgen de Aránzazu	1
Trias i Pujol	1
S. Juan de Alicante	1

The disease-free supervival rate, based on criteria of histological response, was 62% for good responders and 44% when the response was poor.

Protocol of the Spanish Society of Pediatric Oncology-Osteosarcoma-2001

Based on these results, in 2001 a new protocol was elaborated to continue a complete, up-to-date Spanish registry of all pediatric patients with OS, to treat localized OS and metastatic OS differently and shortening treatment duration, decreasing the total dosis of methotrexate, in light of the results (similar to those of the SEOP 95) published by other treatment groups who use fewer doses of methotrexate and, thereby adapt the dosis of methotrexate on the basis of individual pharmacokinetics, to achieve optimal therapeutic levels. Furthermore, molecular biolgy studies were initiated to evaluate prognostic correlation.

The chemotherapy schedule for cases of localized disease consisted of:

Iphosphamide (1,800 mg/ m^2 IV, in 1h, 5 days) (weeks 0 and 5).

Adryamycin (25 mg/ m^2 IV, in 18h, 3 days) (weeks 0, 5 and 10).

Methotrexate (12 g/ m^2 IV, in 4h, 1 day) (weeks 3, 4, 8, 9, 13, 14).

Table 2 Local relapse 9/ 100 (9%)

Localization	Patients
Distal femur	4
Fibula	2
Proximal tibia	1
Proximal humerus	1
Iliac	1
Coinservative surgery	9
Necrosis	>90% 8
	<90% 1
Phase of treatment	Following surgery: 1
	Out of treatment: 8

Table 3 Spanish Society of Pediatric Oncology-Osteosarcoma-2001-Localized

Hospital	Patients
Niño Jesús	15
Virgen del Rocío	12
Sant Pau	13
Sant Joan de Déu	6
La Paz	6
12 de Octubre	4
Carlos Haya	4
La Fe	3
Miguel Servet	3
Ramón y Cajal	2
Vall d'Hebron	2
Cruces	2
Gregorio Marañón	2
Trias i Pujol	2
Virgen del Camino	2
Central de Asturias	2
Universitario de Canarias	1
Ntra. Sra. de la Candelaria	1
Sabadell	1
Juan Canalejo	1
Virgen de Arrixaca	1
Xeral de Galicia	1
Torre Cárdenas	1
Total	97

Table 4 Spanish Society of Pediatric Oncology-Osteosarcoma-2001-Metastatic

Hospital	Patients
Sant Pau	6
Niño Jesús	4
S. Joan de Déu	3
Maternoinfantil de Málaga	1
La Fe	1
Trias i Pujol	1
Valle d'Hebron	1
Universitario de Canarias	1
Total	18

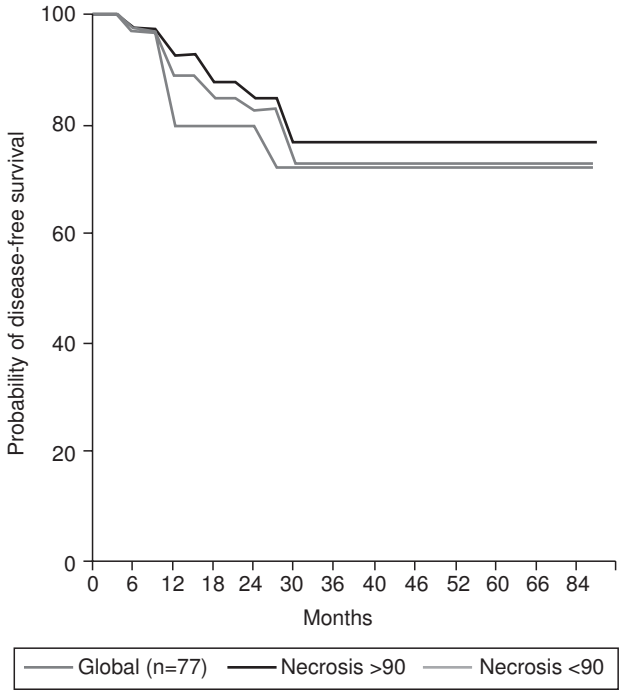

Figure 4 Spanish Society of Pediatric Oncology-Osteosarcoma-2001. Disease-free supervival.

Cisplatin (120 mg/m^2, in 4h, 1 day) (week 10).

At week 15, surgery was peformed and postoperative chemotherapy consisted of:

Iphosphamide (1,800 mg/m^2 IV, in 1h, 5 days) (weeks 17, 21, 29, 33).
Adryamycin (25 mg/m^2 IV, in 18h, 3 days) (weeks 17, 21, 25).
Methotrexate (12 g/m^2 IV, in 4h, 1 day) (weeks 20, 24, 28, 32, 36).
Cisplatin (120 mg/m^2, in 4h, 1 day) (weeks 25, 37).

In patients with metastasis at the time of diagnosis, surgery was indicated at week 11, after having received two cycles of iphosphamide and adryamycin, three cycles of methotrexate, and one cycle of cisplatin and adryamycin. After surgery, maintenance chemotherapy was followed up to week 32, when chemotherapy was intensified with carboplatin, thiotepa and etoposide, followed by TASPE. The patients included up to March 2008 in the SEOP-OS-2001 protocol are presented in the tables 3 and 4.

Overall survival was 73%; in patients with a degree of necrosis greater than 90%, it was 77% and in patients with necrosis of less than 90%, it was 72%, although the protocol remains open and toxicity is being evaluated and changes are being considered with regard to the route of drug administration to decrease short- and long-term side effects (fig. 4).

Conflict of interests

The authors state that they have no conflict of interests.

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