ORIGINAL RESEARCH

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# Malignant bone tumors in Pediatrics. Five year experience in a pediatric referral center

## *Tumores óseos malignos en pediatría. Experiencia de cinco años en un centro de referencia pediátrico*

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| Abstract |

**Background:** Osteosarcoma (OS) and Ewing's Sarcoma (ES) are the two most common malignant bone tumors in children. A retrospective review of the records of children diagnosed in a pediatric hospital over a five year period (2008-2013) was performed.

**Objective:** To present the experiences acquired during the treatment of these types of tumors and to compare the results obtained with those reported in the literature.

**Methodology:** The database of the Oncology and Pathology Service of Fundación Hospital de la Misericordia (HOMI) was reviewed to identify patients with primary bone tumors referred for histopathology analysis.

**Results:** 22 patients were diagnosed with OS, with a mean age of 11.9 years. 96% of cases were located in the lower extremities. All patients received neoadjuvant chemotherapy and 86% underwent surgical treatment; 13% survived. 15 patients were diagnosed with ES, with a mean age of 12.4 years. 67% of cases were located in flat bones, 53% of patients had metastasis when diagnosed, and all received neoadjuvant chemotherapy. 40% of patients received surgical intervention and 20% received radiotherapy. Survival at the completion of the reseearch was 33%.

**Conclusions:** Cure and survival rates are lower than those reported in the literature despite efforts to improve treatments.

**Keywords:** Osteosarcoma; Ewing's Sarcoma; Disease Progression; Recurrence; Neoplasm Metastasis (MeSH).

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| Resumen |

**Introducción.** El osteosarcoma (OS) y el sarcoma de Ewing (SE) son los tumores óseos malignos más frecuentes en edad pediátrica. En el presente estudio se realiza la revisión de los tumores malignos primarios de hueso diagnosticados en un hospital pediátrico de referencia en un período de cinco años (2008-2013).

**Objetivos.** Mostrar la experiencia en el tratamiento de osteosarcomas y sarcomas de Ewing y comparar los resultados con lo reportado en la literatura.

**Materiales y métodos.** Se revisó la base de datos del Servicio de Oncología y Patología de la Fundación Hospital de la Misericordia (HOMI) para identificar los pacientes con tumores primarios de hueso remitidos para estudio histopatológico.

**Resultados.** 22 pacientes con edad promedio de 11.9 años tuvieron diagnóstico de OS; 96% de los casos se localizaron en la extremidad inferior, 100% de los pacientes recibieron quimioterapia neoadyuvante, 86% recibieron manejo quirúrgico y 13% sobrevivieron. 15 pacientes con edad promedio de 12.4 años tuvieron diagnóstico de SE; 67% de los casos se localizaron en huesos planos, 53% de los pacientes presentaron metástasis al diagnóstico, 100% recibieron quimioterapia neoadyuvante, 40% fueron llevados a cirugía y 20% recibieron radioterapia. La sobrevida fue de 33% al finalizar esta investigación.

**Conclusiones.** Las tasas de curación y sobrevida son menores a las reportadas en la literatura a pesar de esfuerzos en mejorar los tratamientos.

**Palabras clave:** Osteosarcoma; Sarcoma de Ewing; Progresión de la enfermedad; Recurrencia; Metástasis de la neoplasia (DeCS).

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## Introduction

Osteosarcoma (OS) and Ewing's sarcoma (ES) are the most common malignant bone tumors in children. OS is a mesenchymal tumor characterized by osteoid production; it occurs at all ages but is more common in children, with an estimate yearly incidence of 3.9 white children per million and 4.5 million African American children per million, and a similar distribution in men and women (1). Most osteosarcomas occur during the first two decades of life and the coincidence of OS with the pubertal peak implies a cause-effect relationship between accelerated bone growth and malignant transformation (2). Other factors that may support this relationship are, on the one hand, the predilection of OS for the metaphyseal of fast growing bones like the distal femur, the proximal tibia and the proximal humerus and, on the other, its earlier appearance in girls than in boys, coinciding with earlier pubertal development (3).

The second most common malignant bone tumor in children and young adults worldwide is ES. It belongs to the Ewing family of tumors/primitive neuroectodermal tumors (PNET), which, in turn, includes bone and extraosseous ES, Askin tumor of the chest wall and PNET. ES shows a slight male predilection, with a male:female ratio of 1.2:1 (4,5). Unlike OS, most ES occur in the flat bones of the axial skeleton, particularly the pelvis and costal arches; when they occur in long bones, they tend to compromise the diaphysis of bones and are more common in the femur, tibia and fibula.

Genetic mutations play a major role in the onset of both types of tumors. Patients with hereditary retinoblastoma have up to 1 000 times more risk of developing an OS due to germline mutations in the Rb gene. Moreover, the loss of heterozygosity, structural rearrangements or specific mutations of the gene are present in 60-70% of sporadic OS (6). Abnormalities in genes that regulate the cell cycle, such as p53, p16, Cyclin D1, MDM2, among others, have been implicated in the genesis of non-hereditary OS (7).

Evidence proves that OS presents greater chromosomal rearrangements with an average alteration of one for every 10Mpb. Recently, the phenomenon of chromothripsis or rearrangement of hundreds of genomic portions of the same chromosome produced by a single event, which is frequent in bone tumors (25%) and particularly in OS (3), was described. Contrarily, ES is characterized by the presence of a relatively simple karyotype, with few numerical and structural aberrations; in 85% of cases, a reciprocal translocation between chromosome 11 and 22t (11:22) is seen, which is why it is considered a pathognomonic disease (4).

The clinical picture is similar for both tumors: the main symptom is pain and usually inflammation or swelling at the site of the lesion; often, patients experience lameness and occasional pathological fractures. That the patient mentions a predominantly minor trauma related to the appearance of clinical manifestations is not unusual. Systemic symptoms such as fever and weight loss are rare in OS, but in ES, they can be associated with increased erythrocyte sedimentation rate (ESR), mild anemia or leukocytosis. The presence of increased serum lactate dehydrogenase (LDH) levels has been correlated with tumor severity and worse prognosis (4,8).

In the diagnostic approach to bone tumors, anteroposterior and lateral radiographies in the site of the lesion show changes in bone density, like the diaphyseal osteolysis in ES and lytic, sclerotic or mixed metaphyseal lesions in OS, usually accompanied, in both cases, with cortical ruptures and periosteal reaction with extension to soft tissues —in over 90% of cases of OS and ES— (5). Nuclear magnetic resonance (NMR) is optimal to assess bone involvement caused by the tumor and the presence of joint and vascular involvement, as well as "skip" metastasis and infiltration to adjacent soft tissues (3,5,8). CAT scan is the best method to determine lung metastases in the extension study.

Pulmonary metastases are evident in the images of 20% of the patients with OS at the moment of diagnosis and microscopic metastases may be found in 80% of the cases (9). Similarly, up to 25% of patients with ES develop metastatic disease, especially in the lungs, and other common locations such as bone and bone marrow. Spreading to lymph nodes, liver or central nervous system is rare in both entities (4,5,8). All patients who have a confirmed diagnosis of bone OS or ES are advised to take a high resolution computed tomography (CT) in the chest to look for pulmonary lesions; in the case of ES, a bilateral aspirate and biopsy of the bone marrow, and a bone scintigraphy with $Tc^{99}$ or PET-FDG are also performed to search for bone marrow or bone metastases (4).

OS treatment begins with induction or neoadjuvant chemotherapy, followed by surgery, ideally with the purpose of rescuing or preserving the limbs, and finalizes with post-surgical chemotherapy. There are several therapeutic schemes that involve combinations of drugs such as doxorubicin, high doses of methotrexate, cisplatin and ifosfamide, carboplatin and etoposide, and their average duration ranges from 35 to 40 weeks. Event free survival rate is 70% (10) and overall survival rate is 80% at five years (11) with the use of neoadjuvant chemotherapy or induction chemotherapy.

Previously, ES was treated with surgery or isolated radiotherapy and had a very high mortality rate, so the use of adjuvant chemotherapy was proposed; in consequence, current protocols combine chemotherapy, local control of the disease and, in some cases, radiotherapy (6).

The drugs currently used for treating the localized disease are ifosfamide, etoposide, cyclophosphamide, doxorubicin, vincristine and actinomycin, which are administered in cycles every two weeks; remarkable improvement of event-free survival at five years, for up to 73% of patients, has been achieved (12,13).

For both tumors, using neoadjuvant chemotherapy facilitates surgery and augments the possibilities of saving the limbs, because the number of candidate patients for salvage surgery increases as a result of the reduction of the initial tumor size. The surgical approach has a significant influence on the probability of cure and survival of long-term patients and chemotherapy helps controlling micrometastases by diminishing the risk of recurrence. The goals of surgery are to remove the tumor and to maintain the greatest possible functionality of the limb, but the local control can only be achieved with wide resection margins, which, sometimes in unresectable tumors, imply amputation or disarticulation of the limbs (14).

Preserving the limbs with resected bone reconstruction, using various techniques such as autologous, vascularized or not grafts and allografts usually found in bone banks, and stents that may be expandable, should be attempted as much as possible (4,14).

Unlike OS, ES tumor is sensitive to radiation, so radiotherapy plays an important role in the treatment of inoperable tumors since the objective is to reduce their size and make them resectable; similarly, it is useful for patients with para-spinal masses, which constitutes an urgency due to neurological involvement. Postoperative radiotherapy is recommended for resected tumors with positive margins or low necrosis, and is also used for palliation in cases of recurrent disease and for patients with lung metastases at initial diagnosis (8).

The presence of metastasis is the most important adverse prognostic factor for OS; when detected during the diagnosis, the

survival rate decreases up to 30% (11). Similarly, for patients with metastatic ES, prognosis is adverse; different studies have shown that increasing standard chemotherapy does not improve the outcome (12) and even raises the risk of toxicity and secondary malignancies (15), achieving free-event survivals at five years of only 22% (12).

The degree of response of the primary tumor to preoperative chemotherapy as a prognostic factor has also been exposed in several studies (16). For both OS and ES, tumor necrosis percentage of the surgical specimen is measured. Patients with better prognosis are those whose necrosis is higher than 90% of the tumor, and are denominated responders (3). The latest reports indicate that the best response will be shown by patients diagnosed with OS and necrosis of 100% (17).

Some recurrence is found in 30 to 40% of patients with OS and ES (18); 80% of patients with OS relapse in their lungs, either in a combined or isolated way, and the remaining 20% relapse in other sites, including the bones. Local recurrence is 5% (11) and the survival rate at five years after a recurrence is only 10-13% in patients with ES (18,19).

This study aims at describing the characteristics and the experience gained while managing such tumors at Fundación HOMI in Bogota, since there are no similar reports in Colombia.

## Materials and methods

The database of the Oncology and Pathology Service of Fundación HOMI in Bogota was reviewed to identify patients with primary bone tumors referred for histopathology between May 2008 and May 2013. Authorization from the ethics committee of the institution was obtained prior to the review of the database and the principle of privacy and confidentiality was preserved.

This study included children between 1 and 18 years old at diagnosis. Patients with OS received a protocol with ifosfamide, doxorubicin and cisplatin until 2012, and then, the possibility of measuring levels of methotrexate in the institution arose, so it was added in high doses ($12g/m^2$) to the treatment. Patients with ES received a protocol with ifosfamide, etoposide, doxorubicin, cyclophosphamide, vincristine and actinomycin. Patients who did not continue with the treatment in the institution were excluded since follow up could not be performed. Once pathology reports were confirmed, a review of medical records was conducted.

## Results

40 patients were found in the database, but three were excluded because they did not continue with treatment in the institution. Of 37 patients included in the study, 22 (59%) were diagnosed with OS and 15 (41%) with ES; no other primary malignant bone tumor was found. The characteristics of patients, both with OS and ES, are described in Table 1.

### Osteosarcoma

The average age at diagnosis was 11.9. All tumors were located in long bones, 96% of them in the lower limbs. At diagnosis, lactate dehydrogenase (LDH) was requested to 18 patients with OS and the value ranged between 288 and 4492 mg/dl. 50% of these patients had high levels (greater than 500). Simple radiography was abnormal in 95% of cases. CT was taken to some patients and confirmation was obtained through a NMR in all cases.

20 of the 22 patients with OS were taken to surgery between three and eight months after diagnosis, nine patients were amputated (55%) and 11 underwent salvage surgery (45%). Two patients did not receive surgical treatment because their disease progressed during treatment and died. The pathology study reported 100% necrosis of the tumor in three patients while they were alive (Table 2) and, among them, one patient presented metastatic disease at diagnosis with survival rate of 36 months. Mortality was 78% among patients with post-chemotherapy necrosis below 90% (non-responders).

**Table 1.** Characteristics of patients diagnosed with osteosarcoma and Ewing's sarcoma.

| Characteristics | | Osteosarcoma n (%) | Ewing's sarcoma n (%) |
|---|---|---|---|
| Gender | Total Patients | 22 (59) | 15 (41) |
| | Male | 12 (54) | 9 (60) |
| | Female | 10 (46) | 6 (40) |
| Primary tumor localization | Femur | 14 (64) | 1 (7) |
| | Tibia | 7 (32) | 5 (33) |
| | Humerus | 1 (4) | - |
| | Vertebra | - | 3 (20) |
| | Pelvis | - | 2 (13) |
| | Costal arch | - | 2 (13) |
| | Astragalus | - | 1 (7) |
| | Boulder | - | 1 (7) |
| Reason for consultation | Pain | 21 (95) | 13 (87) |
| | Edema | 9 (40) | 3 (20) |
| | Mass | 4 (18) | 4 (27) |
| | Trauma | 9 (40) | 2 (13) |
| | Limitation | 5 (22) | 1 (7) |
| | Pathological fracture | 1 (4) | 1 (7) |

Source: Own elaboration based on the data obtained in the study.

**Table 2.** Responsiveness to chemotherapy of the primary tumor in living patients with osteosarcoma.

| | n 16 (%) | Alive |
|---|---|---|
| Stage I | 2 (13%) | 0 |
| Stage IIA | 3 (19%) | 0 |
| Stage IIB | 5 (30%) | 1 |
| Stage III | 3 (19%) | 2 |
| Stage IV | 3 (19%) | 3 |

Source: Own elaboration based on the data obtained in the study.

Of the 22 patients, seven (32%) had metastasis at diagnosis, all in lungs. The overall survival of patients with metastasis at diagnosis was 28% and ranged from 10 to 36 months, while for those without metastasis was 40% and ranged from 12 to 40 months.

10 of these patients (45%) had disease progression, and four presented lung metastases at diagnosis. The most common site of progression was the lung (58%), followed by local progression (32%) and other sites such as brain and liver (11%). Seven of the patients whose disease progressed during treatment (70%) died between 1 and 13 months later; two of them were not monitored.

The recurrence of the disease of seven patients (32%) was documented: six of them died between 6 to 12 months after the diagnosis. One was not monitored.

At the time of the study, a total of five treated patients diagnosed with OS (22%) were alive.

### Ewing's sarcoma

The average age at diagnosis was 12.4 years. Although the most common location of the primary tumor was the flat bones, the primary location for 33% of them was the tibia. Eight patients with metastasis at diagnosis (53%) — four located in the lung (50%), two in bone marrow and bone (25%), one in lung and bone (12.5%) and bone (12.5%)— were included in this study (Table 1).

At diagnosis, the leukocyte count was between 6 240 and 22 160; the leukocyte count for 35% was higher than 11 000 and 13% of patients had anemia at diagnosis. LDH was requested to 10 patients and the value ranged between 160 and 2 169; 60% of them had high levels.

Simple radiography was abnormal for 63% of patients; CT was taken for some of them and, in all cases, the diagnosis was obtained using NMR.

6 of the 15 patients diagnosed with ES (40%) underwent surgery, which took place three to eight months after diagnosis. 5 out of 6 patients (84%) underwent salvage surgery and 1 out of 6 (16%) underwent amputation. The remaining nine patients (60%) were not suitable for surgery due to tumor localization. The pathology study of patients undergoing surgery showed necrosis of 100% of the tumor in three of them, between 90% and 99% in one and less than 90% in two. Among the operated patients, three had metastasis at diagnosis; two of them were good respondents (necrosis 100%) but despite this, they died between 17 to 32 months after diagnosis; a non-respondent patient died eight months after diagnosis. The remaining three operated patients and two of the nine unoperated patients were alive by the end of this investigation.

Out of the 15 patients diagnosed with ES, eight presented metastases at diagnosis and survival ranged between 8 to 32 months, while those without metastases survived between 3 and 55 months.

Disease progressed in four patients (27%); three showed progression in the form of lung metastases, one presented metastases since the moment of diagnosis and all of them died within 2 to 3 months after progression.

Five patients (33%) had disease recurrence: two died within two months, one of them with multiple metastases, one died two years later, one is receiving second-line treatment and the other receives palliative treatment.

## Discussion

The characteristics of the patients evaluated, in terms of tumor location, are very similar to those reported in the literature, which states that the most common primary site for OS is the femur, and for ES is the flat bones. However, it is noteworthy that 33% of cases of ES were located in the tibia and vertebral involvement ranked second in number, exceeding the frequency of location in pelvis and ribs. All patients presented pain as an initial common symptom, nevertheless, this is not a specific sign of this type of tumors.

Initial laboratory studies show that 35% of children with ES had leukocytosis at diagnosis. 50% of patients with OS and 60% of patients with ES had elevated levels of LDH. 75% of OS and 80% of ES patients, that passed away, had elevated levels of LDH at diagnosis, confirming the worst prognosis influenced by this factor (4,8).

Regarding imaging studies, the sensitivity of plain radiography was good for patients with OS —95% of the studies reported the lesion— while the performance for ES was much lower —only 63% of the studies were reported as abnormal— thus, turning plain radiography into a great diagnosing tool at primary levels of care, where patients initially consult and where the suspected diagnosis appears. For all patients, diagnosed suspicion was confirmed through MRI, which is ideal for assessing local tumor involvement (3,5,8). In the extension study, tomography is the best method to confirm the presence of lung metastases (4).

In this series, the incidence of metastasis was higher than that reported in the literature, with rates of 32% for patients with OS and 53% with ES, which might suggest that diagnosis is made at a later stage. Location at lungs and metastases at diagnosis were found for all patients with OS, while only 50% of patients with ES experienced it, noting involvement of other bones and bone marrow instead.

All treatment modalities, such as chemotherapy or radiation therapy and surgery aim at controlling micrometastases, achieving adequate necrosis, decreasing tumor size and locally controlling the disease, thus reducing the possibilities of recurrence. All patients received neoadjuvant chemotherapy and 20% of patients received radiotherapy.

Of the 22 patients with OS, 20 were taken to surgery, 11 of them with limb preservation; however, with ES, the experience was less encouraging as only 6 out of 15 patients could be surgically treated and only five limbs were salvaged. Of patients with OS, 3 of the 20 taken to surgery had necrosis of 100% and all were alive at the time of the study; one of them even had metastases at diagnosis. Although the degree of necrosis constitutes a prognostic factor, 2 of the 3 patients with 100% necrosis died.

The progression of the disease was established during treatment and became another adverse prognostic factor. 45% of patients with OS and 27% with ES had disease progression, which was directly related to poor survival. OS patients died between 1 and 13 months after the diagnosis of disease progression, whereas those who were diagnosed with progressive ES died between 2 and 3 months later.

Relapse rates reported in the literature range between 30% and 40% with a mortality of 80-90% (18,19). These figures are similar to the findings in this investigation, in which, on the one hand, 32% of cases of OS relapsed and all of them died within three years and, on the other, 33% of patients with ES relapsed; three of them died before two years and two were alive and being controlled upon completion of the study.

Although patients have clinical manifestations and usual location that could lead to a rapid diagnosis of the disease, usually, proper diagnosis takes longer, therefore, there is a delay in the therapeutic approach; this situation contributes to lower cure and survival rates than those reported in the literature despite efforts to improve treatments.

## Conflict of interests

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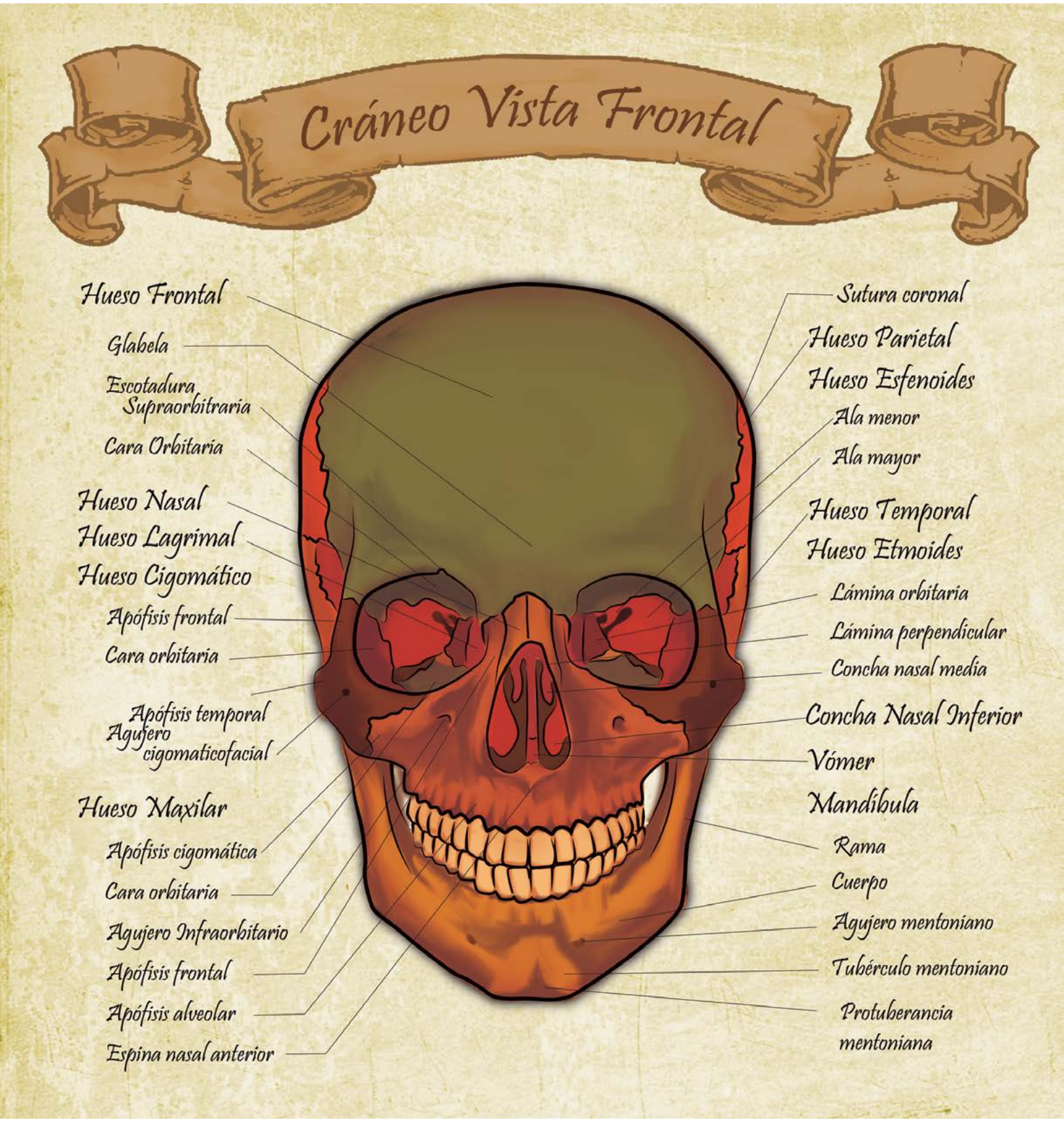
## References


1. **Ottaviani G, Jaffe N.** The epidemiology of osteosarcoma. *Cancer Treat. Res.* 2009;152:3-13. http://doi.org/cd575k.
2. **Bassin EB, Wypij D, Davis RB, Mittleman MA.** Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes Control.* 2006;17(4):421-8. http://doi.org/fmgvm8.
3. **Gorlick R, Khanna C.** Osteosarcoma. *J. Bone Miner. Res.* 2010;25(4):683-91. http://doi.org/fm2thf.
4. **Pizzo PA, Poplack DG.** Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
5. **Potratz J, Dirksen U, Jürgens H, Craft A.** Ewing sarcoma: clinical state-of-the-art. *Pediatr. Hematol. Oncol.* 2012;29(1):1-11. http://doi.org/fzxrh9.
6. **Ritter J, Bielack SS.** Osteosarcoma. *Ann. Oncol.* 2010;21(Suppl 7):vii320-5. http://doi.org/csbnvg.
7. **Broadhead ML, Clark JC, Myers DE, Dass CR, Choong PF.** The molecular pathogenesis of osteosarcoma: A review. Sarcoma. 2011;2011:1-12. http://doi.org/fcckmd.
8. **Lanzkowsky P.** Manual of pediatric hematology and oncology. 5th ed. Oxford: Elsevier; 2011
9. **Messerschmitt PJ, García RM, Abdul-Karim FW, Greenfield EM, Getty PJ.** Osteosarcoma. *J. Am. Acad. Orthop. Surg.* 2009;17(8):515-27. http://doi.org/bjgz.
10. **Ando K, Heymann MF, Stresing V, Mori K, Rédini F, Heymann D.** Current therapeutic strategies and novel approaches in osteosarcoma. *Cancers.* 2013;5(2):591-616. http://doi.org/bjg2.
11. **Mirabello L, Troisi RJ, Savage SA.** Osteosarcoma incidence and survival rates from 1973 to 2004: data from the surveillance, epidemiology, and end results program. *Cancer.* 2009;115(7):1531-43. http://doi.org/d2dxrc.
12. **Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, *et al.*** Addition of ifosfamide and etoposide to standard chemotherapy for ewing's sarcoma and primitive neuroectodermal tumor of bone. *N. Engl. J. Med.* 2003;348(8):694-701. http://doi.org/c8qcd5.
13. **Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, *et al.*** Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group. *J. Clin. Oncol.* 2012;30(33):4148-54. http://doi.org/bjg3.
14. **Grimer RJ.** Surgical options for children with osteosarcoma. *Lancet Oncology.* 2005;6(2):85-92. http://doi.org/czs2fh.
15. **Goorin AM, Schwartzentruber DJ, Devidas M, Gebhardt MC, Ayala AG, Harris MB, *et al.*** Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. *J. Clin. Oncol.* 2003;21(8):1574-80. http://doi.org/bdj4xj.
16. **Ta HT, Dass CR, Choong PF, Dunstan DE.** Osteosarcoma treatment: State of the art. *Cancer Metastasis Rev.* 2009;28(1-2):247-63. http://doi.org/dr975f.
17. **Min HS, Kang HG, Ro JY.** Therapy Related Changes in Osteosarcoma and Ewing Sarcoma of Bone. *The Open Pathology Journal.* 2009;3(2):99-105. http://doi.org/bkzc79.
18. **Leavey PJ, Mascarenhas L, Marina N, Chen Z, Krailo M, Miser J, *et al.*** Prognostic Factors for Patients With Ewing Sarcoma (EWS) at First Recurrence Following Multi-Modality Therapy: A Report From the Children's Oncology Group. *Pediatr. Blood Cancer.* 2008;51(3):334-8. http://doi.org/cn5wjj.
19. **Balamuth NJ, Womer RB.** Ewing's sarcoma. *Lancet Oncol.* 2010;11(2):184-92. http://doi.org/b4bcg7.

# Cráneo Vista Frontal





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