

Osteosarcoma in pre-adolescents: diagnostic interval, metastasis frequency, and treatment abandonment

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Abstract

Background: osteosarcoma is the most common malignant bone tumor, but it is rare before adolescence. The clinical behavior of the tumor that develops in pre-adolescents may differ from that seen during adolescence. **Method:** This is a retrospective study of pre-adolescents with osteosarcoma diagnosed in a tertiary-level hospital. The patients were compared with adolescents diagnosed during the same period. **Results:** we analyzed 149 patients (forty-four pre-adolescents). The diagnostic interval median was 7 weeks in pre-adolescents and 12 weeks in adolescents ($p = 0.002$). Forty-four patients had metastases at diagnosis (ten pre-adolescents) ($p = 0.23$). Limb-salvage surgery was performed on sixteen patients (two pre-adolescents). Fifty-six patients (thirteen pre-adolescents) abandoned the treatment ($p = 0.18$). Overall survival was 63 months in pre-adolescents and 52 months in adolescents ($p = 0.301$). **Conclusion:** We only found differences in the diagnostic interval, which was shorter in pre-adolescent patients. Studies with a larger number of pre-adolescents are necessary to determine the differences in the characteristics of the disease in adolescent patients.

Keywords: Osteosarcoma. Metastases. Pre-adolescents. Treatment abandonment. Survival.

Osteosarcoma en pre-adolescentes: intervalo diagnóstico, frecuencia de metástasis y abandono del tratamiento

Resumen

Introducción: El osteosarcoma es el tumor óseo maligno más común, y es raro antes de la adolescencia. El comportamiento clínico del tumor que se desarrolla en preadolescentes puede ser diferente del observado en adolescentes. **Método:** Estudio retrospectivo de preadolescentes con osteosarcoma diagnosticados en un hospital de tercer nivel. Los pacientes fueron comparados con adolescentes diagnosticados durante el mismo periodo. **Resultados:** Se analizaron 149 pacientes (44 preadolescentes). La mediana del intervalo diagnóstico fue de 7 semanas en preadolescentes y 12 semanas en adolescentes ($p = 0.002$). Presentaron metástasis al diagnóstico 44 pacientes (10 preadolescentes) ($p = 0.23$). Se realizó cirugía de salvamento de extremidad a 16 pacientes (2 preadolescentes). Abandonaron el tratamiento 56 pacientes (13 preadolescentes) ($p = 0.18$). La supervivencia global fue de 63 meses en preadolescentes y 52 meses en adolescentes ($p = 0.301$). **Conclusiones:** Solo se encontró diferencia en el intervalo diagnóstico, que resultó más corto en los pacientes preadoles-

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centes. Son necesarios estudios con mayor número de preadolescentes para conocer las diferencias en las características de la enfermedad respecto a los pacientes adolescentes.

Palabras clave: Osteosarcoma. Metástasis. Preadolescentes. Abandono del tratamiento. Supervivencia.

Introduction

Osteosarcoma is the most frequent malignant bone tumor. It has a bimodal age distribution, with the first and highest peak appearing during adolescence and the second peak in adults over 65¹. In adolescents, osteosarcoma is associated with a growth spurt, usually located in appendicular bones, and has a more favorable prognosis than in adults².

The occurrence of osteosarcoma in patients before adolescence is relatively rare, accounting for only 1.9 cases/million. Limited information is available about this disease in this age group. Due to the distinct physiological characteristics of pre-adolescent patients compared to adolescents, the clinical behavior of this tumor may vary depending on the age at which it is diagnosed, potentially leading to different outcomes during adolescence. The National Cancer Institute investigators in the USA have reported differences in the genetic profile between both groups³.

To know the characteristics of the disease in pre-adolescents, a cohort of patients under 10 years old was analyzed and compared to adolescents diagnosed in 20 years in a tertiary-level medical center.

Definition of terms

PREADOLESCENTS

We defined pre-adolescent patients as those < 10 years at diagnosis. The age of ten was arbitrarily selected as a cutoff point to include only pre-adolescent patients. This was based on the knowledge that the pubertal growth spurt occurs at 11 years for boys and 10 years for girls⁴.

DIAGNOSTIC INTERVAL

It was defined as the time elapsed in weeks between the beginning of the signs and symptoms and the diagnosis of the tumor.

TREATMENT ABANDONMENT

We defined it as missing ≥ 4 consecutive weeks of the desired treatment after the initiation. This excluded

decisions by primary oncologists for palliative treatment, having a patient status inappropriate to receive the treatment, such as infection causing delayed treatment, or discontinuing the treatment due to toxicity⁵.

Method

The study was conducted in a tertiary-level medical center that treats the pediatric population of the west of the country and receives patients from eleven states. In 2023, the Department of Oncology had 642 in-hospital discharged patients.

The clinical records of the patients diagnosed with osteosarcoma during the period from 2000 to 2020 were inspected in search of the following variables: gender, date of diagnosis, age at diagnosis, diagnostic interval, location, histology of the tumor, presence of metastases at diagnosis, local control performed surgery (radical or limb-salvage), treatment abandonment, date of the last follow-up and patient status at this time.

The medical records with diagnostics delivered by the pathology department were included, along with the results of the initial extension studies (nuclear magnetic resonance of the affected region, pulmonary computerized axial tomography of high resolution, and bone scintigraphy). According to the reports of these studies, the patients were classified as metastatic or non-metastatic disease. To compare the patients, they were divided into pre-adolescents and adolescents.

Statistical analysis

Frequencies and percentages for categorical variables, medians, and interquartile range (IQR) for continuous variables. In inferential statistics, χ^2 was used for the bivariate analysis of categorical variables, U-Mann Whitney for continuous variables, and odds ratio (OR) as a measure of association. Overall survival (OS) was calculated through the Kaplan-Meier method, defined as the elapsed time from the date of diagnosis to the last follow-up date or death by any cause. To analyze the effect of age, the Log-rank test was used. A statistically significant difference was considered as $p < 0.05$. The statistics program Statistical Packages for the

Table 1. Patients' demographics and clinical characteristics

Patients characteristics	Total (n = 149)	Pre-adolescent patients (n = 44)	Adolescent patients (n = 105)	p
Sex				
Male	77	23	54	1.0
Female	72	21	51	
Age (years)				
Median (IQR)	12 (3.9)	8.1 (2.0)	13.0 (2.34)	0.00
Diagnostic interval (weeks)				
Median (IQR)	8 (12)	7 (8)	12 (10)	0.03
Location				
Limbs	141	44	97	0.10
Axial	8	0	8	
Histology				
Osteoblastic	84	31	53	0.16
Chondroblastic	42	8	34	
Fibroblastic	13	3	10	
Telangiectatic	10	2	8	
Stage at diagnosis				
Metastatic	44	10	34	0.23
Non metastatic	105	34	71	
Treatment abandonment				
Yes	56	13	43	0.18
No	93	31	62	

IQR: interquartile range.

Social Sciences V25 processed information. The hospital's ethics and Investigation committees approved the study with authorization number R-2019-1302-017, dated February 25, 2019. As this is routinely collected data for clinical care, waiver of consent was approved.

Results

In the analyzed period, 161 patients were diagnosed with osteosarcoma. However, twelve medical records were not located; hence, they were excluded from the study. Altogether, 149 patients' information was analyzed. The median age at diagnosis was 12 years (IQR 3.96), and the median diagnostic interval was 8 weeks (IQR 12). Metastases at diagnosis were observed in forty-four patients (29%): thirty-eight in the lung, four in other bones, and two in both lung and bones. We didn't find differences in the diagnostic interval between patients with metastatic (median 8 weeks; IQR six) and no metastatic disease (median 11 weeks; IQR twelve) ($p = 0.323$).

Local control surgery was performed on 109 patients (73%): ninety-three (85%) underwent radical surgery, and sixteen (15%) underwent limb-salvage surgery. Forty (27%) patients did not undergo radical surgery as

the parents of thirty-seven (93%) did not approve of the procedure, and three (8%) had already been amputated at the time of their hospital admission. Fifty-six (38%) patients abandoned treatment, thirty-seven (66%) of them before surgery.

Pre-adolescent patients

Forty-four were pre-adolescent patients, with a median age at diagnosis of 8 years (IQR = 2.0) and a median diagnostic interval of 7 weeks (IQR = 8). Ten (23%) had metastatic disease at the time of diagnosis. Radical surgery was performed in thirty-two patients (73%), and limb salvage surgery in only two. Thirteen (30%) patients abandoned treatment.

In [table 1](#), patients' demographics and clinical characteristics are compared. As can be seen, we only found a difference in the diagnostic interval, which was shorter in pre-adolescent patients. While the frequency of metastatic disease at the time of diagnosis (OR = 0.61; 95% confidence interval [CI] = 0.25-1.48), treatment abandonment (OR = 0.60; 95% CI = 0.25-1.35), and OS (63 months in pre-adolescent patients, standard deviation (SD) 7.92; vs. 52 months in adolescent patients; SD 5.51) ($p = 0.301$) were similar ([Fig. 1](#)).

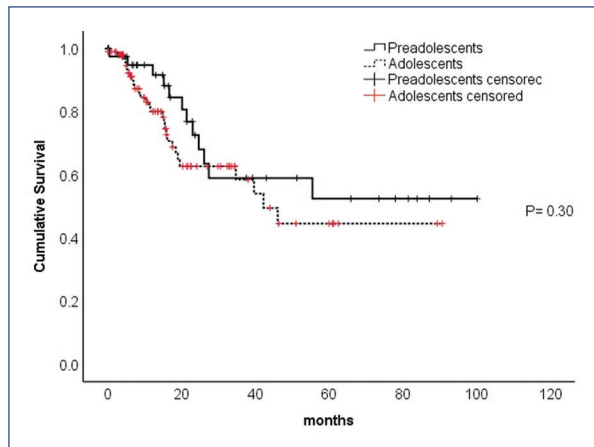


Figure 1. Overall survival curves.

Discussion

Osteosarcoma is a malignant bone tumor characterized by the formation of osteoid material. Its highest peak incidence occurs during adolescence. Given its rarity, the disease that occurs before adolescence—when the physiological characteristics differ from adolescents—has been less studied.

In this article, we defined preadolescence according to the definition of Rytting et al.⁴, which has subsequently been used by other authors⁶⁻⁸. We only found a difference in the diagnostic interval between both groups, which was shorter in pre-adolescent patients. (7 vs. 12 weeks). However, the frequency of metastatic disease was similar to that in adolescent patients. Even though it is logical to suppose that a shorter diagnostic interval is associated with less advanced disease, it has been debated concerning osteosarcoma: Lawrenz found no association between diagnostic interval and metastasis frequency after the analysis of 1,792 patients (346 with metastasis)⁹. Yang et al. also found no relationship between both variables in a fifty-one-child cohort¹⁰. Finally, Brasse did not find a relation between diagnostic interval and metastasis¹¹. However, none of these studies analyzed pre-adolescents separately. Recently, It has been reported that tumor biology is even more important than social factors in determining the diagnostic interval in bone sarcomas¹².

The number of pre-adolescent patients analyzed in the present study prevents us from establishing a conclusion regarding the relationship between diagnostic interval and frequency of metastasis. Still, the presence of metastatic disease in some patients compels us to

maintain a high level of suspicion in a pre-adolescent patient with persistent bone pain.

Mirabello et al.³ found the highest carrier frequency of pathogenic/likely pathogenic variant in a cancer susceptibility gene in 24.5% of patients aged 0-10 years with osteosarcoma, but studies with a large number of pre-adolescent patients are required to know if these differences influence the behavior of osteosarcoma diagnosed within the first decade of life¹³.

During the period analyzed, two chemotherapy regimens were used: from 2000 to 2017, a protocol consisting of cisplatin, doxorubicin, cyclophosphamide, and etoposide was applied. Starting in 2018, the protocol of ifosfamide, carboplatin, and doxorubicin was utilized¹⁴. All patients received the current treatment protocol at the time of diagnosis, irrespective of age and stage of the disease. Although we did not observe a difference in survival, the high treatment abandonment rate prevents us from comparing the effectiveness of these treatment regimens in both groups.

The treatment abandonment of almost 40% observed in this study is higher than the reported in Central America (30%)¹⁵ and Southeast Asia (19.7%)¹⁶, where the researchers considered that the cause was the rejection of radical surgery since, as in the present study, most of the patients abandoned treatment before performing surgery. In our country, the implementation of strategies to diminish the abandonment of treatment is urgent in patients with osteosarcoma, given the negative impact it represents on their survival.

The current study has some limitations. The retrospective design needs to be revised to verify the reliability and certainty of the information collected from clinical records. In addition, the number of included patients cannot provide statistical solid power. However, to our knowledge, this is one of the series with the most significant number of pre-adolescents with osteosarcoma. In addition, the study does not consider parameters such as lactate dehydrogenase, alkaline phosphatase, or post-neoadjuvant residual tumor percentage, which could support differences in the tumor's biological behavior. It is essential to carry out studies with a more significant number of pre-adolescent patients with osteosarcoma to learn about the behavior of the tumor diagnosed within the first decade of life.

Conclusion

We found differences only in the diagnostic interval, which was shorter in pre-adolescent patients. More

extensive studies involving pre-adolescents with osteosarcoma are necessary to understand the disease characteristics in adolescent patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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