

# Epidemiological study of cancer in adolescents at a referral center

*Estudo epidemiológico de câncer na adolescência em centro de referência*

*Estudio epidemiológico de cáncer en la adolescencia en centro de referencia*

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## ABSTRACT

**Objective:** To analyze the epidemiological characteristics of adolescents with cancer referred to an oncologic center, between 2000 and 2006.

**Methods:** A retrospective descriptive study was carried out in order to evaluate the epidemiological data of patients aged between ten and 19 years at diagnosis and admitted at the Institute of Oncology (IOP/Graacc) of Universidade Federal de São Paulo, Brazil, between 2000 and 2006.

**Results:** Among 2,362 patients admitted during this period with a diagnosis of cancer, 629 (26.6%) were adolescents. Mean age was 13.7 years, being 56.8% male. Regarding race, 60.7% of the patients were white, 30% mulattoes, 6.5% blacks, and 2.5% of patients had no characterization of race in the medical records. The most frequent types of tumors were: central nervous system tumors (22.1%), osteosarcoma (14.6%), lymphoma (14.5%), and leukemia (14.5%). The overall survival at five years was 73.7%. Adolescents with the diagnosis of rhabdomyosarcoma presented disseminated disease and histology of worse prognosis, which contributed for increasing the mortality rate of this group of patients.

**Conclusions:** Adolescents with cancer are a group of patients with distinct characteristics when compared to other cancer groups. Our results show differences in the prevalence of tumors

during adolescence and childhood, in the later leukemias and central nervous system tumors predominate. It is crucial to facilitate the access of adolescents to oncologic centers in order to provide early diagnosis and proper treatment.

**Key-words:** adolescent; neoplasm; epidemiology.

## RESUMO

**Objetivo:** Analisar as características epidemiológicas dos adolescentes portadores de neoplasias encaminhados para o Instituto de Oncologia Pediátrica (IOP/GRAACC) da Universidade Federal de São Paulo, entre os anos de 2000 a 2006.

**Métodos:** Trata-se de um estudo retrospectivo descritivo, em que foram avaliados os dados epidemiológicos dos pacientes, com idade entre dez e 19 anos ao diagnóstico, admitidos do ano 2000 a 2006 no IOP/Graacc.

**Resultados:** Do total de 2.362 pacientes admitidos neste período com diagnóstico de câncer, 629 (26,6%) eram adolescentes. A idade média encontrada foi de 13,8 anos, sendo a maioria do sexo masculino (56,8%). Em relação à raça, 60,7% dos pacientes eram brancos. Os tipos de tumores mais frequentes foram: tumores de sistema nervoso central (22,1%), oste-

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Conflito de interesse: nada a declarar

Recebido em: 30/12/2010

Aprovado em: 17/8/2011

ossarcoma (14,6%), linfomas (14,5%) e leucemias (14,5%). A sobrevivida global, em cinco anos, dos 629 pacientes deste estudo foi de 73,7%. Destaca-se que os adolescentes com rabiomiossarcoma apresentavam doença disseminada e histologia de pior prognóstico, contribuindo para o aumento na taxa de mortalidade deste grupo de pacientes.

**Conclusões:** Os adolescentes com câncer correspondem a um grupo de pacientes que apresenta características peculiares quando comparado a outros grupos oncológicos. Há diferença histológica dos tumores dos adolescentes com os da infância, em que predominam leucemias e tumores do sistema nervoso central. Nesse contexto, é fundamental facilitar o acesso desses pacientes a centros especializados e oferecer meios apropriados para o diagnóstico precoce e tratamento adequado.

**Palavras-chaves:** adolescente; neoplasias; epidemiologia.

## RESUMEN

**Objetivo:** Analizar las características epidemiológicas de los adolescentes portadores de neoplasias encaminados al Instituto de Oncología Pediátrica (IOP/GRAACC) de la Universidad Federal de São Paulo, entre los años 2000 a 2006.

**Métodos:** Se trata de un estudio retrospectivo descriptivo, en el que fueron evaluados los datos epidemiológicos de los pacientes, con edad entre 10 y 19 años al diagnóstico, admitidos entre los años de 2000 y 2006 en el IOP/GRAACC.

**Resultados:** Del total de 2.362 pacientes admitidos en ese periodo con diagnóstico de cáncer, 629 (26,6%) eran adolescentes. El promedio de edad fue de 13,8 años, siendo la mayoría del sexo masculino (56,8%). Respecto a la raza, 60,7% de los pacientes eran blancos. Los tipos de tumores más frecuentes fueron: tumores de sistema nervioso central (22,1%), osteosarcoma (14,6%), linfomas (14,5%) y leucemias (14,5%). La sobrevivida global en cinco años de los 629 pacientes de este estudio fue de 73,7%. Se subraya que los adolescentes con rabiomiossarcoma admitidos al presente estudio presentaban enfermedad diseminada e histología de peor prognosis, contribuyendo al aumento en la tasa de mortalidad de este grupo de pacientes.

**Conclusiones:** Los adolescentes con cáncer corresponden a un grupo de pacientes que presenta características peculiares si comparados a otros grupos oncológicos. Hay diferencia histológica de los tumores de los adolescentes con los de la infancia, en que predominan leucemias y tumores del sistema nervioso central. En ese contexto, es fundamental facilitar el acceso de esos

pacientes a centros especializados y ofrecer medios apropiados al diagnóstico temprano y tratamiento adecuado.

**Palabras clave:** adolescente; neoplasias; epidemiología.

## Introduction

Cancer is a social problem that does not only affect the patients themselves, but also impacts on their families and communities. It is rarely diagnosed in adolescence<sup>(1)</sup> and demands careful and complex management by health professionals. Despite all of the advances that have been achieved in oncology, there are still many questions to be answered in relation to cancer in adolescents<sup>(2)</sup>.

Studies of cancer in adolescents are rare and difficult to interpret, since epidemiological aspects of cancer in young people are very often analyzed in conjunction with data from children or adults<sup>(2)</sup>. Adolescents with malignant neoplasms have a lower survival rate than other age groups, probably because of problems accessing oncology centers and because healthcare policies focus on children and adults<sup>(2,3)</sup>. In the United States, 94% of cancer patients under the age of 15 years were put on cooperative protocols at specialized centers, whereas only 21% of those aged 15 to 19 were in cooperative groups, demonstrating failure to care for adolescents<sup>(2)</sup>.

In Brazil, malignant neoplasms are one of the principal causes of deaths among adolescents, although external causes (accidents and violence) are even more prevalent in all five of the country's regions. The most common causes of death from cancer are malignant neoplasms of lymphatic and hematopoietic tissues, accounting for around 50% of cancer deaths in the 10–14 years age group and 40% of cancer deaths among 15 to 19-year-olds<sup>(1)</sup>.

The objective of this study was to analyze the epidemiological characteristics of adolescents admitted with neoplasms to a pediatric oncology center. The importance of this study lies in the need to collect data on cancer in adolescents (age, sex, types of tumor and survival rates) in order to better understand the incidence and outcomes of neoplasms in this special group of patients who have their own characteristics and need specialized attention.

## Methods

This was a retrospective descriptive study that analyzed the medical records from 2000 to 2006 for all patients with diagnoses of cancer who were aged 10 to 19 at referral

to a single specialist center, the Pediatric Oncology Institute's Adolescent and Child Cancer Support Group (IOP/Graacc) at the Universidade Federal de São Paulo (Unifesp). The IOP/Graacc is a highly complex center to which children and adolescents from all over Brazil are referred after being diagnosed with cancer, at a rate of 300 new cases per year.

Epidemiological data such as age, sex and race were recorded, in addition to type of tumor, presence/absence of metastasis, clinical stage and survival for the entire sample. Secondary neoplasms diagnosed during the period were also analyzed. Cases were excluded if the primary tumor was diagnosed at an age younger than 10 or older than 19 years or if the cases were related to relapsed primary tumors originally diagnosed before the patient was 10. All patients were treated according to the pediatric treatment protocols used at the institution during the study period and were cared for by a multidisciplinary team.

The statistical analysis was conducted using database software (Excel) and statistical programs such as SPSS 11.5. Frequencies were analyzed and the Kaplan-Meier method was used to analyze outcomes. This study was approved by the Research Ethics Committee at Unifesp.

## Results

A total of 2,362 patients were admitted between 2000 to 2006 with cancer diagnoses and 629 (26.6%) of them were adolescents.

The adolescents' mean age was 13.8 years, 59.6% of cases were in the 10–14 age group and 40.4% were aged 15 to 19. When the different types of neoplasm were stratified by age, it was observed that osteosarcomas (bone tumors) and non-rhabdomyosarcoma soft tissue sarcomas occurred at a higher rate in the 15 to 19 age group; rhabdomyosarcoma soft tissue tumors were evenly distributed by age; and all other types of tumor had higher incidence from 10 to 14 years of age (Figure 1).

With regard to sex distribution, 357 (56.8%) of the sample were male and 272 (43.2%) were female. There was a greater incidence of the principal tumor types among males. With regard to skin color/race, 60.7% of the patients studied were white, 30.0% had brown skin, 6.5% were black and 2.5% of patients' medical race did not contain any indication of race.

The principal tumor types observed in these adolescents, by order of frequency, were as follows: tumors of the central nervous system (CNS) (22.1%), osteosarcomas (14.6%), lymphomas (14.5%), leukemias (14.3%), Ewing family

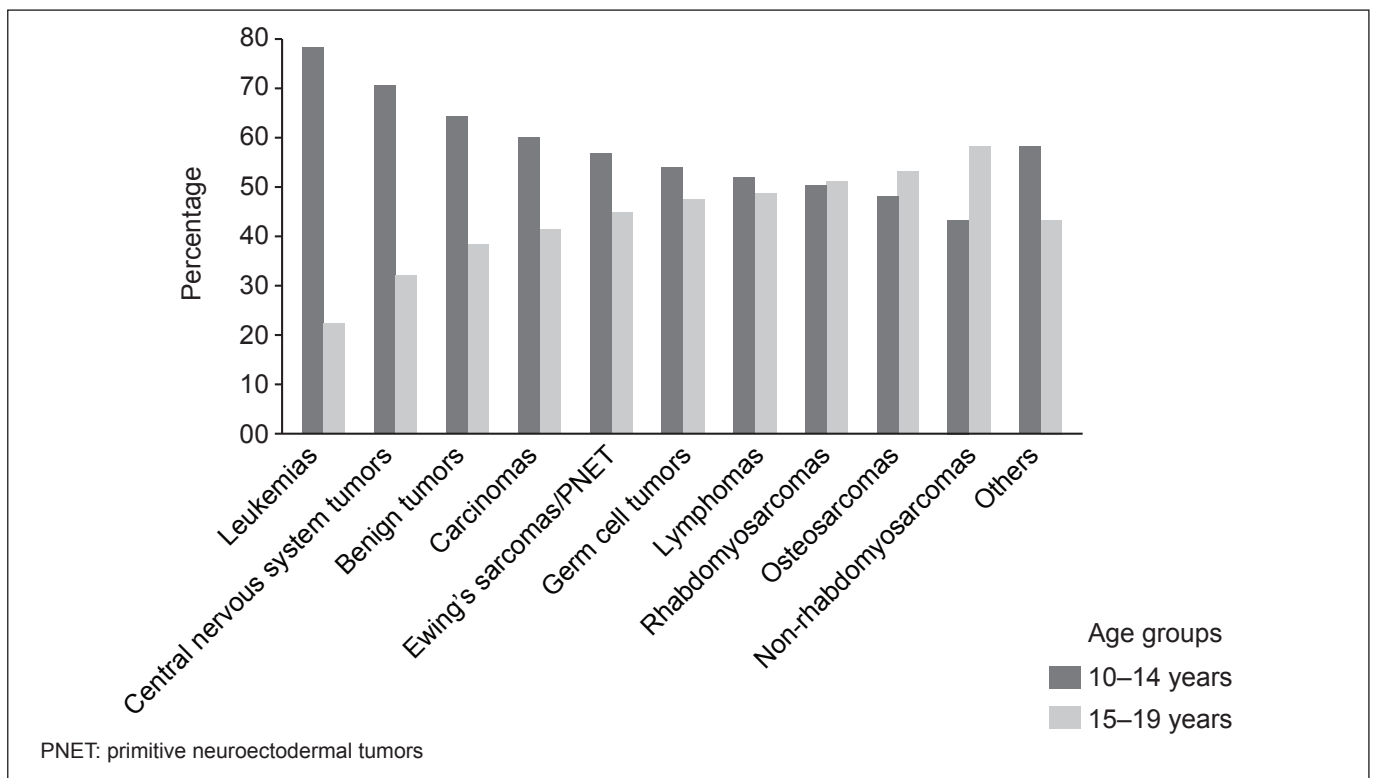


Figure 1 - Relationship between age group and neoplasm type

tumors/primitive neuroectodermal tumors (PNET); (7.1%), germ cell tumors (5.9%), non-rhabdomyosarcoma sarcomas (5.6%), carcinomas (4.6%) and others.

In this study, CNS tumors were the most common type of cancer, accounting for 22.1% (139/629) of cases. The most common subtypes of CNS tumor were: astrocytomas 38.8% (54/139), medulloblastomas 15.8% (22/139), craniopharyngiomas 15.1% (21/139) and germ cell tumors 11.5% (16/139). The majority of CNS tumors had onset when patients were between 10 and 14 years old (69.1% of cases). Males accounted for 61.8% of CNS tumor cases.

There was a greater number of malignant bone tumors than benign ones (137 cases – 87.8%) and osteosarcoma was the most common type of malignant bone tumor (92/137 – 67.1%). Osteosarcoma patients were evenly distributed across the two age groups, with 47.8% in the 10 to 14 age group and 52.2% in the 15 to 19 group, and 59.8% of patients with this type of bone tumor were male. The most common osteosarcoma sites were: femur (46.7%), tibia (23.9%) and humerus (9.8%). Pulmonary metastasis was detected in 37.8% of these patients at the time of diagnosis. Ewing’s sarcomas accounted for 32.8% (45/137) of bone tumors, 55.6% of these cases were in the 10 to 14 age group and more females were affected than males (53.3%). The pelvis was the primary site of 26.7% of Ewing’s sarcoma cases, with 22.2% in the femur, 13.3% in the tibia and 37.8% in other sites (Figure 2). At the time of diagnosis, pulmonary metastasis incidence among patients with Ewing’s sarcoma was already at 35.6%.

In this study, 14.4% of cases were lymphomas (91/629), 63.7% of which were Hodgkin’s lymphomas (HL) and 36.3% non-Hodgkin’s lymphomas (NHL). It was observed that 55.2% of the 58 cases of HL were in the 15 to 19 age group, 56.9% were male and 56.9% were initially staged at I/II. The 10 to 14 age group contained 63.6% of the 33 cases of NHL and NHL incidence was greater among males (60.6%). The NHLs were diagnosed at advanced stages: 80.6% of cases were stage III/IV, while 19.4% were stage I/II (Figure 3).

There were 90 cases of leukemia among the adolescents: 61.1% were acute lymphoid leukemia (ALL), 31.1% were acute myeloid leukemia (AML) and 7.8% were chronic myeloid leukemia (CML). Among the adolescents with ALL, 78.2% were aged 10 to 14 years and 58.2% were male; 71.4% of the AML patients were aged 10 to 14 years and 53.6% were female whereas all of the CML cases were detected at ages between 10 and 14 and 85.7% of these patients were male.

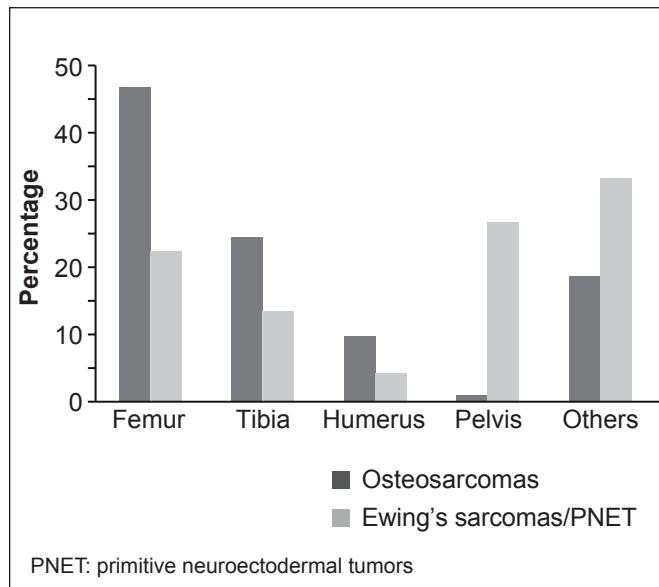


Figure 2 - Relationships between primary site and bone tumor type

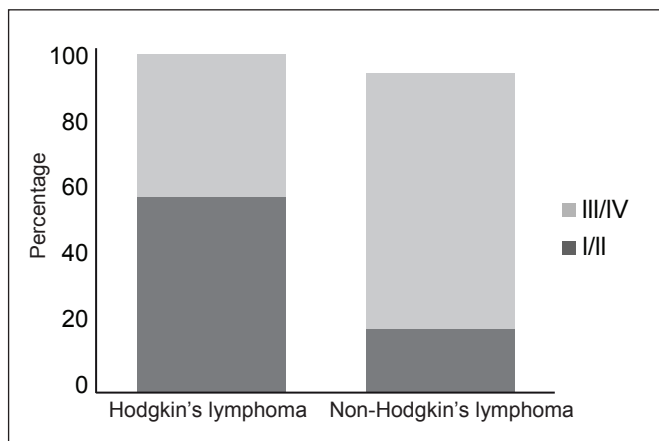
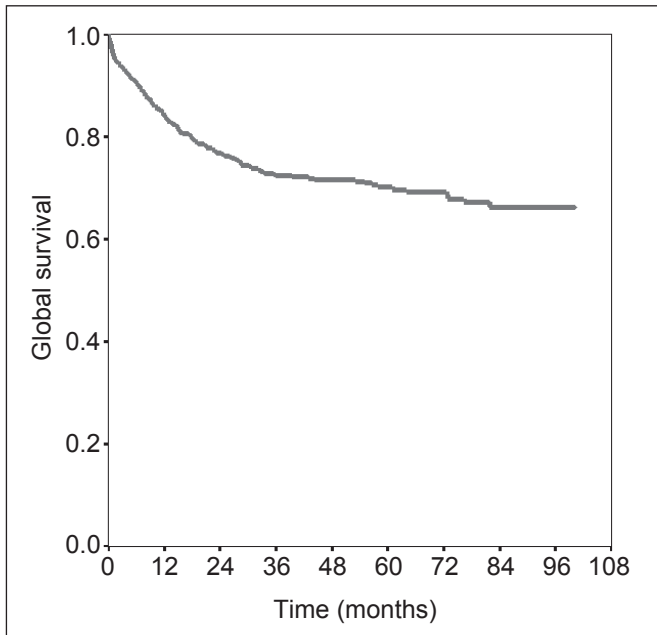


Figure 3 - Tumor stages of Hodgkin's lymphomas and non-Hodgkin's lymphomas

Projected global 5-year survival, estimated by Kaplan-Meier survival analysis of all 629 patients in the study, was 73.74% (Figure 4).

### Discussion

Incidence of malignant neoplasms increases gradually after 10 years of age. Cancer diagnosis rates are around three times greater after the age of 15 than before this age<sup>(3)</sup>. In this study, 26.6% (629/2362) of the patients admitted to our referral center were adolescents. This could be an underestimation, however, since only one third of adolescents with cancer get to pediatric oncology centers<sup>(2)</sup>.



**Figure 4** - Global 5-year survival of the 629 adolescents with cancer

Lymphomas are the most frequent malignant tumors among adolescents, followed by leukemias, CNS tumors and bone tumors<sup>(3-5)</sup>. The most common types of tumor found in our patients were as follows: CNS tumors, bone tumors, lymphomas and leukemias. It was to be expected that our results would diverge from the literature, since this study was conducted at a specialist CNS and bone tumor treatment center.

Our sample of adolescents was 56.8% male (357). Data on the relationship between tumor incidence and sex in this age group are divergent, but males seem to be affected more often<sup>(6-8)</sup>.

Epidemiological studies have shown that among adolescents cancer is 50% more common in the 15 to 19 year age group than among 10 to 15-year-olds, with 203 new cases per million people<sup>(9-11)</sup>. However, the average age observed in this study was 13.7 years and just 40.4% of the adolescents were aged 15 to 19. This divergence from published data is probably because the study was conducted at a single pediatric institution and therefore suffers from bias introduced by sampling only patients referred to the oncology center in question.

When associations between neoplasm type and age were analyzed, it was observed that osteosarcomas and non-rhabdomyosarcoma sarcomas were the only tumor types that occurred with greater frequency in the 15 to 19 age group, which was expected since this class of tumors has greater incidence among adolescents and young adults.

In Brazil, analysis of the incidence of tumors with relation to race can be subject to an important bias resulting from racial admixture and data harvested from medical records are subject to the subjectivity of those responsible for completing them. Despite this, the findings of our study are comparable with the literature, since 60.7% of the patients studied were white. Studies have shown that there is a clear difference between whites and blacks in terms of the incidence of tumors; in general whites have higher incidence rates<sup>(5,12)</sup>.

In our study CNS tumors were the most common cancer type, accounting for 22.1% (139/629) of cases. Central nervous system tumors primarily affected males at ages from 10 to 14 years, which is in line with the literature<sup>(7)</sup>. Central nervous system tumors include benign and malignant tumors and are an important class of tumors among adolescents<sup>(13)</sup>. In the United States, CNS tumors are the second most common pediatric tumor<sup>(13)</sup> and the seventh most common tumor type among people 15 to 29 years old<sup>(7)</sup>. These tumors and their treatments are responsible for significant morbidity, including physical deficiencies and neuropsychological and neuroendocrine sequelae. They are also one of the principle causes of cancer mortality among the pediatric population and young adults.

Onset of bone tumors is associated with periods in which there is rapid bone growth, such as in adolescence. The signs and symptoms of these tumors, such as pain and localized swelling can be confused with traumas, delaying diagnosis. In the United States, malignant bone tumors have an annual incidence of 8.7 cases per million children and adolescents under 20<sup>(8,13,14)</sup>. Peak incidence of malignant primary bone tumors is during the second decade of life and among adolescents 95% of these tumors are osteosarcomas or Ewing's sarcomas<sup>(2,11)</sup>. Osteosarcomas were the most common bone tumor type in our sample (67.2%) and were evenly distributed by age (47.8% were in the 10 to 14 age group). Osteosarcomas are generally located in the metaphyseal regions of long bones; the distal femur, proximal tibia and proximal humerus. This type of tumor is also generally linked with a high degree of malignancy and a high rate of metastasis, particularly in the lungs. According to observations described in the literature, metastases are detected in 15 to 21% of patients, impacting on prognosis<sup>(15-20)</sup>. The presence of metastasis is considered the worst prognostic factor and after both univariate and multivariate analyses less than 20% of such patients achieve 5-year disease-free survival<sup>(18)</sup>. In our study, 37.8% of these patients had pulmonary metastases on diagnosis. This percentage is higher than reports in the literature and may be related to late diagnosis, which makes it more likely that the disease will

have progressed to more advanced stages. The importance of early diagnosis means that when faced with nonspecific initial symptoms, very often related to traumas, pediatricians should be alert to the possibility of neoplasms in children and adolescents with symptoms of persistent bone pain, associated with trauma, and should investigate without delay.

Ewing's sarcomas are the second most common malignant primary neoplasm of the bones and primarily affects patients aged 10 to 30<sup>(13)</sup>. According to a study published by the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS), 56% of a total of 1,426 patients studied were diagnosed at ages between 10 and 20 and 44% of these were over 15. In our study 55.6% of Ewing's sarcoma patients were aged from 10 to 14, probably because the oncology center in question is a pediatric institution. In contrast with the osteosarcomas, incidence was higher among females, at 53.3% of cases. This type of tumor has a greater preference for flat bones than osteosarcomas. The incidence of pulmonary metastases among Ewing's sarcoma patients at the time of diagnosis was similar to that for osteosarcomas, at 35.6% of cases. According to the literature, approximately 25% of patients with Ewing's sarcoma have pulmonary metastasis on diagnosis and this is generally associated with late diagnosis and poor prognosis<sup>(21)</sup>, demonstrating the importance of early diagnosis. These data should serve to highlight certain facts: the center analyzed here is an institution that receives patients from all over Brazil, probably very often months late; probably due to the facts that Ewing's sarcoma is a rare disease with nonspecific initial signs and symptoms and this is an extremely active age group leading to this clinical presentation being undervalued. Irrespective of this, the question remains of whether the increased incidence of pulmonary metastases at the time of diagnosis of bone tumors that is observed in Brazil could have a link to some difference in tumor biology.

Lymphomas are malignant neoplasms of the lymphoid system which can be related to autoimmune, infectious and immunosuppressive causes. The incidence of Hodgkin's lymphomas (HL) in adolescents aged 15 to 19 is around twice that of non-Hodgkin's lymphomas (NHL)<sup>(22)</sup>. In our study, 55.2% of patients with HL had onset at 15 to 19 years of age. In contrast, 63.6% of NHL cases occurred between 10 and 14, confirming findings reported in the literature. It should be pointed out that after diagnosis, in addition to classifying the disease by lymphoma type, it is also important to determine the stage since these data are indispensable to selecting the correct treatment for each patient and estimating their prognosis. In our study, 56.9% of HL cases had

initial staging of I or II at diagnosis. In contrast, NHL cases were diagnosed at more advanced stages, to the extent that at diagnosis 80.6% of cases were staged at III or IV, which is due to the rapid growth of this type of tumor.

Leukemias account for around one third of malignant neoplasms in children and one seventh of tumors in adolescents<sup>(2)</sup>. In our study sample there were 90 leukemia cases in adolescents, 61.1% of them were ALL, 31.1% AML and 7.8% were CML. The incidence of these leukemia subtypes is similar to what is seen in the pediatric age group and contrasts with the picture in adults, among whom the most frequent type is CML<sup>(23,24)</sup>. In the United States, approximately 6,500 children and adolescents under 20 develop acute leukemia each year<sup>(23,24)</sup>. Of the adolescents with ALL in our sample, 78.2% of cases were diagnosed in patients aged 10 to 14, with higher incidence among males (58.2%), which is in line with the literature<sup>(13,23)</sup>. Acute myeloid leukemia incidence is uniform among children, but there is a discrete increase during adolescence<sup>(13)</sup>. Chronic leukemias are rare both in childhood and in adolescence. The most common chronic form that affects this population is CML, which accounts for less than 5% of all leukemias in this age group, equating to approximately one hundred cases per year in the United States pediatric population<sup>(23,24)</sup>. Chronic myeloid leukemia is primarily diagnosed in people between 30 and 50 years old<sup>(24)</sup>. Just 7.8% of all leukemias diagnosed among the adolescents studied here were CML and all of these cases were diagnosed at ages from 10 to 14. No significant differences have been reported in the sex or race distribution of this disease<sup>(24)</sup>. In contrast, even though the small sample size affects the significance of the finding, CML incidence was greater among males, with 85.7% of cases.

Interpretation of different survival rates between age groups is complicated by obstacles such as histological typing, initial staging and follow-up period. Adolescents with leukemia put on pediatric protocols have exhibited better survival rates<sup>(25)</sup>. In contrast, adolescents with tumors that are more common among adults, such as melanoma and thyroid cancer, are better treated at adult oncology centers. More than 80% of cancer mortality in the 15 to 19 age group is the result of four groups of malignant tumors: leukemias/lymphomas, sarcomas, CNS tumors and germ cell tumors. Among the tumors, leukemia is the principal cause of death in the same age group<sup>(12,13)</sup>. Overall mortality for all cases described here was 28.5% (182/637). In general, for all types of tumor, less than half of cases result in death, with the exception of rhabdomyosarcoma, which caused elevated mortality (66.7%). It is likely that these findings are related to the fact that the adolescents with rhabdomyosarcoma enrolled on this study already had

disseminated disease and alveolar histology indicative of poor prognosis at the time of diagnosis. In our sample, the tumor types that resulted in the largest proportions of deaths were rhabdomyosarcoma (12/18), bone tumors (45/82), leukemias (34/56) and CNS tumors (30/109).

With relation to global 5-year survival, studies report values of 72% survival for all types of tumor in all pediatric age groups<sup>(6)</sup>. Kaplan-Meier analysis estimated the global 5-year survival of the 629 patients in this study at 73.7%, which is similar to what is found in the literature, where global survival is 72% at 5 years<sup>(6)</sup>.

With reference to the results of this study, it can be concluded that adolescents with cancer are a group that merits

interest, both because of the incidence and because of their special care requirements, since this group has significant differences in terms of the classification and biological behavior of tumors and there are also differences in terms of clinical presentation, treatment, support and prognosis. Therefore, early diagnosis and access to specialized pediatric or adult oncology centers should be facilitated; while oncology centers must equip themselves to cater for the specific needs of this group of patients, in order to be in a position to offer adequate support and treatment. Finally, it should be pointed out that this study was conducted at a specialist referral center and cooperative multicenter studies are needed to validate the results on a national and international scale.

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