Epidemiological Study of Childhood and Adolescent Cancer in Cascavel Cancer Hospital Uopeccan between 2000 and 2014

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Estudo Epidemiológico do Câncer Infantojuvenil no Hospital de Câncer de Cascavel Uopeccan entre os Anos 2000 e 2014

Estudio Epidemiológico del Cáncer Infantil en el Hospital Oncológico de Cascavel Uopeccan entre 2000 y 2014

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ABSTRACT

Introduction: Hospital-based epidemiological studies on childhood and adolescent cancer are important to show the profile of patients cared by the service. **Objective:** To evaluate the characteristics of cancer patients aged 0-19 years at the Cascavel Cancer Hospital Uopeccan (2000-2014). **Method:** Cross-sectional study that evaluated medical charts for the following outcomes: gender, age, color/race, comorbidities, family history of cancer, household, cancer type, staging, treatment, metastasis, recurrences, patient's status at the end of study. Descriptive statistics, chi-square and Kaplan-Meier were applied. **Results:** Boys were more prevalent (55.2%), age range from 1 to 4 years (36.3%), White (87%), urban household (81.6%), with leukemia (35.83%) and in chemotherapy (50.2%). Metastasis occurred in 16.41% and recurrence in 22.38%. There was no report of family history of cancer in 47% of the charts. Other pathologies were denied in 58.9%. In the end, 55.2% were alive and disease-free. There was a statistically significant association between boys younger than 10 years old with renal tumors and neuroblastoma and older than 10 years with lymphomas and malignant epithelial neoplasms and between the current status of the patient with metastasis, relapses, and staging. **Conclusion:** The patients analyzed in this study were mostly leukemic, males and aged 1-4 years. Global and disease-free survival were, respectively, 70.3% and 71.63%.

Key words: Neoplasms; Child; Adolescent; Epidemiologic Studies; Survival Analysis.

RESUMO

Introdução: Estudos epidemiológicos de base hospitalar sobre o câncer infantojuvenil são importantes para mostrar o perfil dos pacientes assistidos pelo serviço. **Objetivo:** Avaliar o perfil clínico-epidemiológico e a sobrevida de pacientes na faixa etária de 0-19 anos atendidos no Hospital do Câncer de Cascavel Uopeccan (2000-2014). **Método:** Estudo transversal com avaliação de prontuários para os seguintes desfechos: sexo, idade, cor/raça, outras patologias, histórico familiar de câncer, domicílio, tipo da neoplasia, estadiamento, tratamento, metástases, recidivas, situação do paciente ao final da pesquisa. A estatística descritiva e os testes qui-quadrado e Kaplan-Meier foram aplicados. **Resultados:** Observou-se maior frequência para meninos (55,2%), faixa etária de 1-4 anos (36,3%), brancos (87%), domicílio urbano (81,6%), leucemia (35,8%) e quimioterapia (50,2%). Ocorreu metástase em 16,41% e recidiva em 22,38%. Não havia relato de histórico familiar de câncer em 47% dos prontuários. Outras patologias foram negadas em 58,9%. Ao final, 55,2% estavam vivos e sem doença. Houve associação estatisticamente significava entre menores de 10 anos com tumores renais e neuroblastoma; maiores de 10 anos com linfomas e neoplasias epiteliais malignas; e entre a situação atual do paciente com metástase, recidivas e estadiamento. **Conclusão:** Os pacientes analisados na presente pesquisa eram na maioria leucêmicos, do sexo masculino e faixa etária de 1-4 anos. A sobrevida global e a livre de doença foram, respectivamente, de 70,3% e 71,63%.

Palavras-chave: Neoplasias; Criança; Adolescente; Estudos Epidemiológicos; Análise de Sobrevida.

RESUMEN

Introducción: Los estudios epidemiológicos hospitalarios sobre cáncer infantil son importantes para mostrar el perfil de los pacientes atendidos por el servicio. **Objetivo:** Evaluar las características de los pacientes oncológicos de 0-19 años atendidos en el Hospital do Cáncer de Cascavel Uopeccan (2000-2014). **Método:** Estudio transversal que evaluó historias clínicas para los siguientes resultados: sexo, edad, color/raza, comorbilidades, antecedentes familiares de cáncer, domicilio, tipo de cáncer, estadificación, tratamiento, metástasis, recurrencias, situación del paciente al final de la investigación. Se aplicó estadística descriptiva, chi-cuadrado y Kaplan-Meier. **Resultados:** Fueron más prevalentes: niños (55,22%), grupo de edad 1 a 4 años (36,32%), blancos (87,06%), hogares urbanos (81,59%), leucemia (35,83) %) y quimioterapia (50,25%). Hubo metástasis en 16,41% y recidiva en 22,38%. No hubo informes de antecedentes familiares de cáncer en 47% de los pacientes. Se negaron comorbilidades en 58,91%. Al final, 55,23% estaban vivos y sin enfermedad. Hubo asociación estadística entre menores de 10 años con tumores renales y neuroblastoma; mayores 10 años con linfomas y neoplasias epiteliales malignas; e entre la situación del paciente con metástasis, recaídas y estadificación. **Conclusión:** Los pacientes analizados en esta investigación eran en su mayoría leucémicos, varones y de 1 a 4 años. La supervivencia global y libre de enfermedad fueron, respectivamente, 70,3% y 71,63%.

Palabras clave: Neoplasias; Niño; Adolescente; Estudios Epidemiológicos; Análisis de Supervivencia.

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INTRODUCTION

Childhood and adolescent cancer is rare when compared with adult's[1] and despite its low prevalence, is the leading cause of death by disease in the developed world among children older than 1 year of age[2]. In Brazil, it is the first cause of death by disease in the age-range of 1 to 19 years, representing a mean percent of 1% to 4% of the total of malignant tumors[3]. According to the National Cancer Institute José Alencar Gomes da Silva (INCA)[4], for each year of the triennium 2020-2022, 8,460 new cases are anticipated, being 4,310 for males and 4,150 for females.

With this, the evaluation of different time series and geographical regions contribute for the analysis of the prevalence, incidence, survival, and mortality rate of these diseases[5]. Thus, the hospital databases are necessary to know the profile of neoplasms, improvement of the care to the patient, clinical research, and support to medical education[3]. Considering that so far data about childhood and adolescent cancer in the city of Cascavel-PR do not exist, its study and data analysis become relevant.

Childhood and adolescent cancer has a wide morphologic variety and quite peculiar characteristics in relation to the primary site of occurrence, clinical behavior and histogenetic type[6], affecting mainly the hematopoietic and mesenchymal cells[6,7]. These pathologies are divided according to the International Classification of Cancer in Childhood (ICCC)[8] and typically the most incident in children and adolescents in Brazil[3,7,9-12] and in other world regions[13-16], the leukemias, tumors of the central nervous system (CNS) and lymphomas.

Based in the information presented, the aim of this study was to analyze the clinical-epidemiological profile and survival of pediatric patients of the pediatric oncology service of "*Hospital do Câncer de Cascavel Uopeccan*" between 2000 and 2014.

METHOD

Cross-sectional study with evaluation of charts (paper and electronic) of children and adolescents up to 19 years of age diagnosed and treated for primary malignant neoplasm (of any topography) in the "*Hospital de Câncer de Cascavel Uopeccan*", between 2000 and 2014 (required period for calculation of survival).

The pediatric oncology service is the only one in Paraná's Western Region. It covers part of the 5th regional health unit (13 municipalities), full coverage and referral for the 7th, 8th, 9th, 10th, 11th, 12^{th,} and 20th regional health units of Paraná.

All the charts whose diagnosis was confirmed by anatomopathological exams (histopathological and cytopathological), hematologic or complete blood count, surgical exploration, imaging, clinical exam, or any other mean were eligible[7]. Patients with benign tumors or of undetermined behavior (whether benign or malignant) who initiated treatment in another hospital (missed diagnosis report) or transferred before the diagnosis were excluded of the sample.

Data collection was conducted between October 2018 and July 2019. The following variables were evaluated: sex, age of detection of cancer and presence of another pathology. Age-range and race/color were based in INCA classifications[3] (younger than 1 year; 1 to 4; 5 to 9; 10 to 14 and 15 to 19 years) and of the "*Instituto Brasileiro de Geografia e Estatística* (IBGE)"[17] (White, Black, Brown, Yellow and Indigenous), respectively.

The type of neoplasm followed the ICCC-3, based in the International Classification of Diseases (ICD)[8]. Data about clinical staging for solid neoplasms, metastasis at the diagnosis, relapse and treatment utilized [chemotherapy (CT); radiotherapy (RTx); surgery (S); bone marrow transplantation (BMT)] and the status of the patient in the final moment of the research data collection (alive without disease; alive with disease; death by disease or by other causes) were collected as well for analysis of the survival (global and disease-free). Global survival is defined as the length of time the patient continued alive after the diagnosis of the disease and disease-free survival, the period where signs and symptoms of the disease are not detected anymore after a curative treatment.

The data were tabulated in Microsoft Excel (2010) and analyzed for descriptive statistics with the software BioEstat 5.3 (The *Mamirauá* Institute for Sustainable Development) and presented in contingency tables (absolute and relative frequencies).

The chi-square test and the exact test of Fisher were adopted to determine the statistically significant association ($p \leq 0.05$) of the type of neoplasm with sex and age-range. For this analysis, the types of neoplasms subclassified were grouped and compared with the other investigated. The age-ranges were divided in younger and older than 10 years old[9]. The same test was applied to analyze the statistically significant association between the current status of the patient with metastasis, relapses, and clinical staging. At this moment, those who were followed-up for at least five years were considered "alive and without disease" after being deemed cured. The chi-square test was utilized to analyze the statistical association among relapses and clinical staging.

For the calculation of survival (software Bioestat) the Kaplan-Meier test and confidence interval of 95% were utilized. The dates of the beginning and end of the follow-up were considered as diagnosis of the patient and last

information in the chart, respectively. The patients who completed the treatment were characterized as disease-free and those with missing or inconsistent information about health or disease as ill. The relapses were characterized as occurrences. Those who died before the end of the treatment or continued in treatment were disregarded in the calculation of the disease-free survival. July 2019 was established as the limit to follow-up the registers of survival in the charts.

The Institutional Review Board of "*Universidade Estadual do Oeste do Paraná*" (2.958.385) approved the study in compliance with Ordinance 466/12 of the National Health Council[18].

RESULTS

Of the 247 charts provided by Hospital Uopeccan, 46 were excluded: relapses (11); benign tumors (6); the responsible rejected treatment (1); patient not diagnosed, transference (8); treatment began in another hospital (13); died before diagnosis (1); incomplete charts (6). Based in the exclusion and inclusion criteria, 201 were included.

Considering all the cases, men were more affected (n=111; 55.22%) (Table 1). However, the individual evaluation of frequency among sexes and each histogenetic type of neoplasm did not show statistically significant association (p>0.05).

For the age-range of 1-4 years (n=73; 36.32%) (Table 1) higher frequency of childhood and adolescent cancer was found. Comparing minor and older than 10 years of age, statistically significant association was encountered for older than 10 years and reticuloendothelial lymphomas/neoplasms (p=0.0003) and other malignant/melanomas epithelial neoplasms. For under 10 years old, statistically significant association was found with renal tumors (p=0.01) and neuroblastoma/other tumors of peripheral nerve cells (p=0.01).

Among the types of neoplasms, leukemia (n=72; 35.83%) was more frequent, specifically lymphoid (n=63; 87.05% of the leukemias). Next, the lymphomas (n=29;

Table 1. Types of malignant neoplasms distributed by sex and age-range (n=201)

Parameter	Sex				Age-range									
Type of neoplasm	Male		Female		<1		1-4		5-9		10 –14		15-19	
Leukemias	42	20,9%	30	14,9%	*	*	30	14,9%	20	9,5%	10	5,0%	9	4,5%
Myeloproliferative and myelodysplastic diseases	42	20.9%	30	14.9%	*	*	30	14.9%	20	9.5%	10	5.0%	9	4.5%
Reticuloendothelial neoplasms and lymphomas	21	10.4%	8	4.0%	*	*	*	*	7	3.5%	13	6.5%	5	2.5%
CNS, intracranial and intraspinal neoplasms	5	2.5%	6	3.0%	*	*	*	*	5	2.5%	*	*	*	*
Neuroblastoma and other peripheral nerve cells tumors	8	4.0%	8	4.0%	*	*	9	4.5%	*	*	*	*	*	*
Retinoblastoma	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Renal Tumors	6	3.0%	11	5.5%	*	*	8	4.0%	7	3.5%	*	*	*	*
Liver Tumors	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Malignant bone tumors	*	*	5	2.5%	*	*	*	*	*	*	*	*	*	*
Soft tissues and other extra bone sarcomas	10	5.0%	8	4.0%	*	*	8	4.0%	*	*	*	*	*	*
Tumors of germinative cells, trophoblastic tumors, and neoplasms of gonads	5	2.5%	5	2.5%	*	*	*	*	*	*	*	*	*	*
Other malignant epithelial neoplasms and malignant melanomas	8	4.0%	7	3.5%	*	*	*	*	*	*	6	3.0%	*	*
Different and non-specified malignant neoplasms	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total	**111**	**55.2%**	**90**	**44.8%**	**14**	**6.9%**	**73**	**36.3%**	**51**	**25.3%**	**38**	**18.9%**	**25**	**12.4%**

Caption: CNS: Central Nervous System.
(*) values lower than 5 patients per group.

14.42%), specifically Hodgkin (n=19; 65.51% of the lymphomas) and renal tumors (nephroblastoma or Wilms' tumor) (n=17; 8.46%) (Table 1).

The sociodemographic condition of the patients, treatments, and status at the end of data collection are described as follows. White race/color was the most predominant (87%). More than three quarts lived in urban area (81.6%). Other pathologies were encountered in 128 charts (62.7%). Four children (2%) were syndromic, two with Down syndrome and leukemia and other with Wilms' tumor (nephroblastoma) and Beckwitch Wiedemann syndrome. Family history of cancer was found in 108 charts, some of them reported more than one relative affected by the disease and patients with more than one pathology, which justifies the results greater than 100% for these variables. Most underwent CT alone (50.2%) or associated with other therapy (40.3%). The status of the patient was checked and tabulated at the end of the data collection period: 55.2% of them were alive without disease. No information about withdrawal from treatment or loss to follow up was found.

Clinical staging of solid tumors is shown in Table 3. This information should be found in the 129 charts but in 48 of them, this did not occur, therefore, for 81 patients only the clinical staging was determined.

Considering a five-year period, the global survival (n=201) and the disease-free survival (n=130) were, respectively, 70.3% (Graph 1) and 71.63% (Graph 2) because the other patients continued in treatment or died.

Metastasis at the diagnosis was found in 33 (16.41%) patients and 45 (22.38%) relapsed. The present status was associated with relapses (p=0.0004) and to metastases (p=0.01) (chi-square test/exact test of Fisher) (n=108).

Clinical staging was determined for only 81 patients. The chi-square test did not detect significant association between this variable and relapses (p=0.88). However, the exact test of Fisher showed significant association between the patient's status and clinical staging (p=0.0004), for which 46 patients were considered.

DISCUSSION

This study analyzed the clinical-epidemiological profile and survival of pediatric patients at the service of pediatric oncology of "*Hospital do Câncer de Cascavel Uopeccan*", in Paraná's Western Region, which provides care to the population of the city of Cascavel and seven health regional units.

To know the profile of childhood and adolescent cancer in Brazil is relevant to expand effective actions to control the disease and plan the services[3]. Therefore, boys (55.2%), Whites (87%) (Tables 1 and 2) were

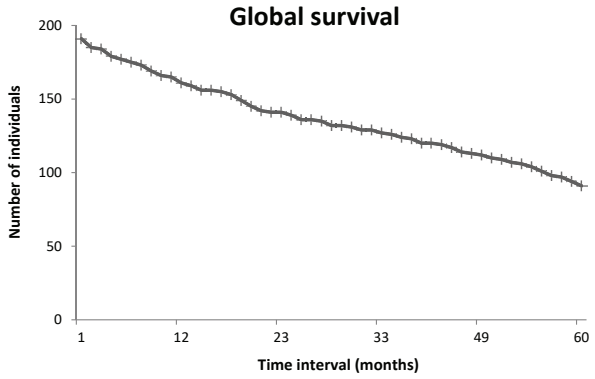
Table 2. Profile of the patients in relation to the sociodemographic condition, treatments, and status at the end of data collection

Parameter	N	%
Race/Skin Color		
White	175	87%
Black	13	6.5%
Brown	10	5%
Yellow	2	1%
Indian	1	0.5%
Residence		
Urban	164	81.6%
Rural	37	18.4%
Presence of other pathologies		
Asthma	1	0.5%
Bronchitis	2	1%
Diabetes	2	1%
Tuberous sclerosis	1	0.5%
Lactose intolerance	1	0.5%
Infantile paralysis	1	0.5%
Nonspecific neurologic lesion	1	0.5%
Nonspecific heart lesion	1	0.5%
Denied	118	57.7%
Family history of cancer		
Grandparents	34	16.9%
Uncles	14	6.97%
Great grandparents	7	3.5%
Parents	5	2.5%
Cousins	5	2.5%
Siblings	5	2.5%
Denied	56	27.9%
Type of treatment		
Chemotherapy	101	50.2%
Chemotherapy + surgery	35	17.4%
Chemotherapy + radiotherapy	24	11.9%
Chemotherapy + radiotherapy + surgery	11	5.5%
Chemotherapy + bone marrow transplantation	8	4%
Chemotherapy + radiotherapy + bone marrow transplantation	3	1.5%
Surgery	10	5%
Radiotherapy	1	0.5%
Surgery + radiotherapy	3	1.5%
Were not treated	5	2.5%
Final status of the patient		
Alive without disease	111	55.2%
Alive with disease	30	14.9%
Death by disease	60	29.9%

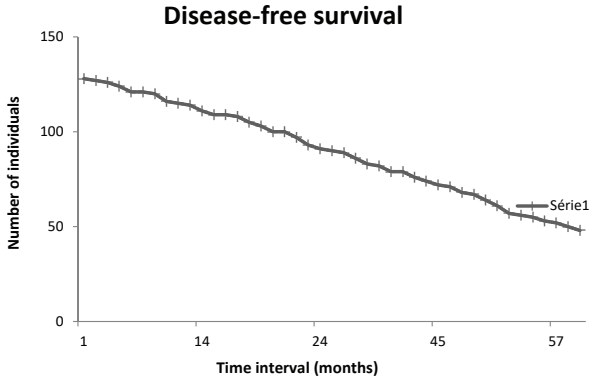
Table 3. Type of solid neoplasm according to the clinical staging (n=129)

Type of neoplasm	Clinical staging										Total	
	I		II		III		IV		NR			
	N	%	N	%	N	%	N	%	N	%	N	%
Reticuloendothelial lymphomas and neoplasms												
Hodgkin's Lymphomas	2	1.5	9	7	3	2.3	5	3.9	0	0	19	14.8
Non-Hodgkin's Lymphomas (except Burkitt lymphoma)	0	0	0	0	3	2.3	1	0.8	2	1.5	6	4.6
Burkitt lymphoma	1	0.8	0	0	0	0	0	0	3	2.3	4	3.1
Central Nervous System and several intracranial and intraspinal neoplasms												
Astrocytoma	0	0	0	0	0	0	0	0	1	0.8	1	0.8
Embryonic intracranial and intraspinal tumors	1	0.8	0	0	0	0	1	0.8	3	2.3	5	3.9
Other intracranial and intraspinal neoplasms	0	0	0	0	0	0	0	0	1	0.8	1	0.8
Nonspecific intracranial and intrapsychic neoplasms	0	0	0	0	1	0.8	0	0	3	2.3	4	3.1
Neuroblastoma and other peripheral nerve cells tumors												
Neuroblastoma and ganglioneuroblastoma	1	0.8	0	0	1	0.8	9	7	5	3.9	16	12.4
Retinoblastoma	0	0	0	0	0	0	0	0	1	0.8	1	0.8
Renal Tumors												
Nephroblastoma and other non-pelvic renal tumors	5	3.9	4	3.1	0	0	6	4.6	2	1.5	17	13.2
Liver Tumors												
Hepatoblastoma	0	0	0	0	0	0	2	1.5	2	1.5	4	3.1
Malignant bone Tumors												
Osteosarcomas	0	0	0	0	0	0	1	0.8	5	3.9	6	4.6
Chondrosarcomas	0	0	0	0	0	0	0	0	1	0.8	1	0.8
Soft tissues and other extra bone sarcomas												
Rhabdomyosarcomas	1	0.8	3	2.3	3	2.3	1	0.8	6	4.6	14	10.9
Other specified soft tissue sarcomas	0	0	0	0	1	0.8	1	0.8	1	0.8	3	2.3
Nonspecific soft tissue sarcomas	0	0	0	0	0	0	0	0	1	0.8	1	0.8
Tumors of germinative cells, trophoblastic tumors, and neoplasms in gonads												
Tumors of intracranial and intraspinal germinative cells	0	0	0	0	0	0	0	0	2	1.5	2	1.5
Malignant tumors of gonadal cells	0	0	3	2.3	2	1.5	1	0.8	2	1.5	8	6.2
Other malignant epithelial neoplasms and malignant melanomas												
Adrenocortical carcinomas	0	0	2	1.5	0	0	1	0.8	4	3.1	7	5.4
Thyroid carcinomas	1	0.8	0	0	1	0.8	0	0	0	0	2	1.5
Melanomas	2	1.5	0	0	0	0	0	0	1	0.8	3	2.3
Other nonspecific carcinomas	1	0.8	0	0	0	0	1	0.8	1	0.8	3	2.3
Different and non-specified malignant neoplasms												
Other malignant specified tumors	0	0	0	0	0	0	0	0	1	0.8	1	0.8
Total	**15**	**11.6**	**21**	**16.3**	**15**	**11.6**	**30**	**23.4**	**48**	**37.1**	**129**	**100**

Caption: NR: no report.



Graph 1. Global survival (n=201)



Graph 2. Disease-free survival (n=130)

predominant in the population investigated. The lack of statistically significant association between sex and type of neoplasm encountered can be explained by the small number of individuals enrolled and the percent difference among sexes. The result of the racial profile was expected because White color is majority in the State of Paraná (65.5%)[17].

The age-range of 1 to 4 years old was the most affected (Table 1) and statistically significant association among the types of neoplasm and age-range was found. It was anticipated the Wilms' tumor and neuroblastoma would be the most frequent in younger than 10 years of age since both are common embryonic tumors in children under 5 years old and their origin are primordial cells which suffered spontaneous mutations and non-mutations acquired by environmental actions[13]. After 10 years of age, typically, they tend to disappear and other cancers become more frequent (lymphomas, carcinomas, germinative cells tumors and bone tumors)[9,13]. The results showed that lymphomas/reticuloendothelial neoplasms and malignant/melanomas epithelial neoplasms are predominant in older than 10 years of age. Lymphomas (specifically Hodgkin), melanomas and carcinomas are more common in adolescents[9,13].

Leukemia was the most frequent neoplasm, particularly the lymphoid type (87% of them) (Table 1). Literature shows that acute lymphoid leukemia (ALL) is more common in children, corresponding to 75% to 80% of the total cases of leukemia[9]. Hodgkin's lymphoma, which affects more the adolescents[13], impacted more than half of the patients (Table 1) and can be related to the number of lymphomas found in older than 10 years (Table 1). Regardless of the possibility of a late diagnosis having been considered as a confounding factor in this analysis, it was attenuated by the amplitude of the division among younger and older than 10 years of age. The third neoplasm more frequent was Wilms' tumor (Table 1) which, in general, is the renal neoplasm more common in childhood. Tumors of the CNS were the sixth in frequency (Table 2).

Most part of the population evaluated in the present study lived in the urban area (Table 2). Paucity of information in the charts about family history of cancer and low frequency of syndromic patients with the disease (2%) were noticed as well. A study demonstrated that, actually, these syndromic patients are but a small portion of the cases of childhood and adolescent cancer[19].

The diagnosis of neoplasm and the stage of the disease determine the therapeutic to be applied[20], and most of the patients underwent CT alone or associated with another modality (Table 2). While inhibiting the cellular proliferation of tumor cells (in myotic phase, preferentially), the chemotherapeutic agents end up by acting in the non-tumor cells as well. Therefore, children (in development and cellular growth) are particularly propense to side effects[21], which justifies studies about the theme.

There are reports about the evolution of the treatments in the last years and the increase of the rates of cure for many types of childhood cancer[1,2,13]. National data present an estimated survival rate of 64% for childhood and adolescent cancer (between zero and 19 years)[3] and 75% in the country's south region[3]. The current study conducted in the same regions showed global survival of 70.3% (Graph 1) and disease-free of 71.63% (Graph 2). This last can be related to the high rate of relapses encountered. It is expected to contribute for the design of future studies in this area and for Population-Base Cancer Registries (PBCR) in Brazil.

It is known that the stage of the disease at the diagnosis[22], metastases, and relapses[1,13,22] can influence survival. The significant association between clinical staging of solid tumors and the current status of the patient reaffirms that the advance of the disease reduces the odds of cure and increase the frequency of sequelae because requires more aggressive treatment[9]. However,

it is possible that biases of information have interfered in these results, mainly because cancer staging is always improving. Metastasis (determinant of the mortality of the patients)[13,22], and relapses (which affect most of all their survival and quality of life)[1] were also significantly associated with the patient status. The non-association between relapses and clinical staging, on the other hand, can be explained by the reduced sample size.

Although the origin of the data analyzed in the current study may have been a limitation factor, the results presented can support the activities in the hospital[3], since the scientific body will have a time series and regional panorama of the population in treatment. Finally, considering the lack of information in many registries, it is suggested the creation of combined protocols to complete the charts to facilitate the collection of information and contribute to carry out other studies, not only in the hospital investigated but in another health services across the country.

CONCLUSION

Most of the patients analyzed in this study were leukemic, with predominance of men and age-range of 1-4 years old. The global and the disease-free survival were, respectively, 70.3% and 71.63%.

CONTRIBUTIONS

All the authors contributed substantially for the study conception/design, collection, analysis and/or interpretation of the data, wording, critical review and approved the final version to be published.

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DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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