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# FOLLOW-UP OF TREATED OSTEOSARCOMA PATIENT

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## ABSTRACT

**Objective:** To evaluate the value of post-treatment follow-up in osteosarcoma patients. **Methods:** Data were collected through a clinical record, with socio-demographic and clinical data, and information relating to the medical appointment. Descriptive analysis of the data was carried out. The Chi-squared test was used to associate the independent variables with attendance at scheduled follow-up appointments. **Results:** We found a recurrence in 59.6% of cases, of which 58% were lung related; 44% presented clinical complaints and arrived on the scheduled date of the appointment. There was no statistically significant association between the demographic characteristics and early attendance of follow-up visits. 81.3% of the cases who came for the appointment earlier than originally scheduled

presented complaints compared to those who did not ( $p=0.005$ ). Of the cases who presented recurrence, 12.9% attended an appointment late and those who did not present recurrence, 47.6% were late for the appointment ( $p=0.006$ ). **Conclusion:** It is seen that the patients who came for an earlier appointment presented more complaints and were associated with the positive result of the exams carried out. The patients who had recurrence and came for an earlier appointment did not present a statistically significant difference in recurrence-free survival. It was observed that distance was not a predominant factor in late attendance at appointments. **Level of Evidence II, Retrospective Study.**

**Keywords:** Osteosarcoma. Bone neoplasms. Recurrence.

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## INTRODUCTION

Childhood cancer is rare and was estimated by the Brazilian National Cancer Institute (INCA), in the biennium 2008/2009, at about 9,890 new cases. In the United States, approximately one out of every 7,000 children from zero to 14 years of age is diagnosed with cancer per year. As is the case in developed countries, in Brazil cancer already represents the second cause of mortality proportionally among children and adolescents aged from 1 to 19 years, in all regions.<sup>1</sup>

Osteosarcoma (OS) is the most common primary malignant bone tumor.<sup>2</sup> It is defined by the presence of malignant mesenchymal cells that produce osteoid or immature bone.<sup>3</sup>

The incidence of OS in the population in general is only 2-3 cases/million people per year, but in adolescents the rate reaches peaks of 8 to 11 cases/million youths aged between 15 and 19 years.<sup>4</sup> In Brazil the estimate is 350 cases/year up to the age of 20 years,<sup>5</sup> corresponding, together with Ewing's sarcoma, to 5% of childhood cancers.<sup>6</sup> In the United States, approximately 560 children and adolescents are affected annually.<sup>7</sup> Information from the population-based cancer records (RCBP) suggests that the incidence of osteosarcoma is higher in the black population

of the USA, Italy, Germany and Spain.<sup>8</sup> In Brazil, the incidence of osteosarcoma, in the age bracket between 10 and 14 years, was higher in the RCBP of São Paulo.<sup>9</sup> At present, the average rate of incidence of childhood cancer in our country is 154.3 per million, with higher rates found in children aged from 1-4 years. Among adolescents from 15-19 years of age, the highest rates are in São Paulo (264 per million), Goiânia (251 per million) and Porto Alegre (229 per million).<sup>10</sup>

Osteosarcoma patients present a survival rate of up to 70% at five years<sup>11</sup> for non-metastatic case and global survival of up to 80%.<sup>12</sup> When they relapse, this survival reaches 20% at one year, and may reach 40% at five years, when complete resection of pulmonary metastases is possible.<sup>13</sup> Most survivors will have good quality of life after adequate treatment; moreover, nowadays the cure does not just target the absence of disease, but a biopsychosocial cure and reduction of the risk of sequelae in the long term.<sup>14</sup>

Therefore, this study aims to evaluate the post-treatment follow-ups of pediatric osteosarcoma patients and to determine the sociodemographic, clinical and treatment-related characteristics that interfere in the post-treatment follow-up of these patients.

All the authors declare that there is no potential conflict of interest referring to this article.

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## MATERIALS AND METHODS

It is a retrospective study carried out at Fundação Pio XII – Hospital de Câncer de Barretos (HCB) with the patients treated for osteosarcoma, by the Pediatric Department in the period between January 2000 and July 2006.

The data were collected through a clinical chart previously defined according to the institution's standards. This chart was completed by the researcher responsible for the study, through a review of the patient's medical records in the Medical Archive and Statistics Service (SAME) of the Hospital. The data were subsequently typed in a specific database, using the Statistical Package for Social Science for Windows version 17.0 (SPSS 17.0). The variables were distributed in categories, and updated with information taken from each clinical chart.

The sociodemographic characteristics were collected from a registration form applied when the patient is admitted to the hospital. The other information was collected after a detailed review of the records. The collection form contained sociodemographic information (sex, ethnic group, age, place of birth, origin and distance), taking distance to mean the time consumed in traveling from the municipality of residence to Hospital de Câncer de Barretos, considered near when less than three hours and far when more than three hours, and clinical information (tumor grade, diagnosis, treatment and patient evolution). The descriptive analysis of the data was performed by means of absolute and relative frequencies, measures of central tendency (mean and median) and dispersion (standard deviation, minimum and maximum). The chi-square test of association was used for the analysis of qualitative variables, while Fisher's exact test was used in the case of the variables that presented boxes with values of less than or equal to five.

The Kaplan-Meier product limit estimator was used in the patient survival analysis, and the comparison of curves was executed using the log rank test. Global survival time was calculated between the end of the treatment and the patient's final status (alive; death). As regards disease-free survival, the time was evaluated between the end of treatment and the appearance of recurrence, emphasizing that only patients without metastasis at the beginning of the study were considered for this analysis. For all the statistical analyses we assumed a descriptive level of 5%. The collected data were typed and analyzed in the SPSS program, version 17.0 for Windows.

The project study was approved by the Institutional Review Board of Hospital de Câncer de Barretos and by the committee of ethics of the School of Medicine of Universidade de São Paulo.

## RESULTS

Of the 52 patients assessed and treated for osteosarcoma, during the follow-up in the Pediatric Department of HCB, 42 were white (80.8%), 32 male (61.5%) and 28 were over 15 years of age (53.8%).

According to origin, in the sample that encompassed eight Brazilian states, namely São Paulo, Rondônia, Minas Gerais, Mato Grosso, Mato Grosso do Sul, Goiás, Alagoas and Piauí, 48.1% of the patients came from the state of São Paulo. As regards mileage, 65.4% of the patients lived far from HCB, i.e., a distance of more than three hours, while 26.9% of the patients spent from 4 to 21 hours traveling to the hospital.

As concerns the clinical characteristics, note that 36 (69.2%) of the patients evaluated did not present metastases upon diagnosis and in the others pulmonary metastasis represented 23.1%, while only 1.9% presented bone metastasis. Of the 52 patients evaluated, 59.6% presented recurrence and among these 34.6% were pulmonary.

### Characteristics of patient appointments

The average quantity of appointments held per patient was 4.8 (sd=3.5), with a maximum of 18 appointments. Among the appointments, 25 were held earlier than the scheduled date, and 23 were held on a later date.

The complaint observed in the appointments was associated with positive radiological examination, while in the appointments where complaints were reported, 53.8% had positive results. On the other hand, of the appointments without reports of complaints, only 17.3% presented positive results ( $p < 0.001$ ). During follow-up, 81.3% of the patients who brought the appointment forward presented some complaint, when compared with those who did not bring the appointment forward, representing a statistically significant association ( $p = 0.005$ ). There was no statistically significant association between the demographic and clinical characteristics and early appearance at the appointment. The presence of recurrence also showed statistically significant association with late attendance to appointments. Of the patients who presented recurrence, 12.9% were late in attending a particular appointment, while among the patients without recurrence, 47.6% were late in attending a particular appointment ( $p = 0.006$ ). The presentation of complaints at any appointment is associated with early attendance at appointments. In the appointments where the patients presented complaints, 35% arranged an earlier appointment, while among the patients who did not present complaints this percentage was 5% ( $p < 0.001$ ). In the appointments where some patients arrived late, 54.5% of the patients were lodging away from home ( $p = 0.010$ ).

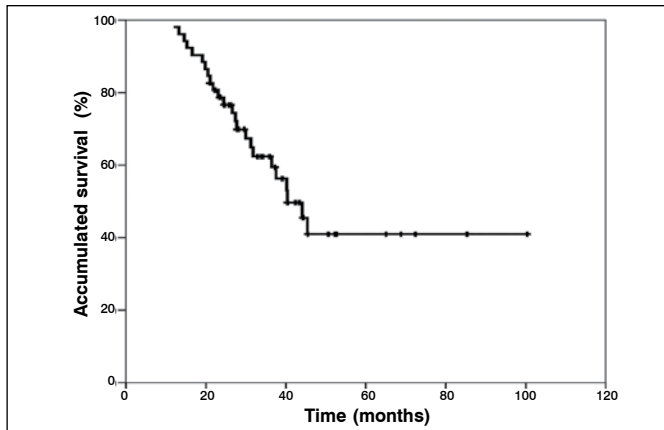
### Analysis of survival

The global survival of the patients seen with osteosarcoma at HCB was 98.1% at 12 months; 78.7% at 24 months; 62.4% at 36 months; and 41% at 60 months. (Figure 1) The event-free survival was 72% at 12 months; 41.4% at 24 months; and 36.2% at 36 and 60 months. (Figure 2)

For the patients with early attendance of appointments, the recurrence-free survival of 12, 24 and 36 months, was 76.9%, 49.9% and 37.4%, respectively. While in the patients who did not attend the appointment early, it was 69.3% at 12 months; 36.6% at 24 and 36 months, not presenting statistically significant difference ( $p = 0.625$ ). (Figure 3)

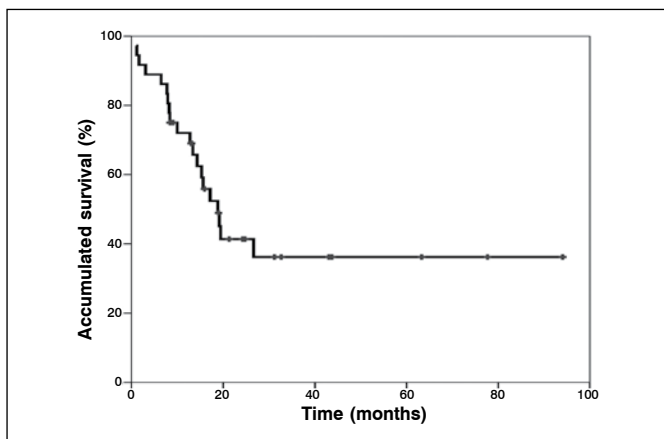
## DISCUSSION

The follow-up of the selected patients was performed by the same medical team and took place in a specialized hospital, with multidisciplinary training, use of equipment of controlled quality, reliable imaging exams and conditions for application of a single treatment protocol, contributing to the data reliability. There are also disadvantages such as the likely bias, since the evaluation involves preexistent data from medical records, submitting to the risks of incomplete annotation. Another disadvantage is the small number of patients involved in the study.



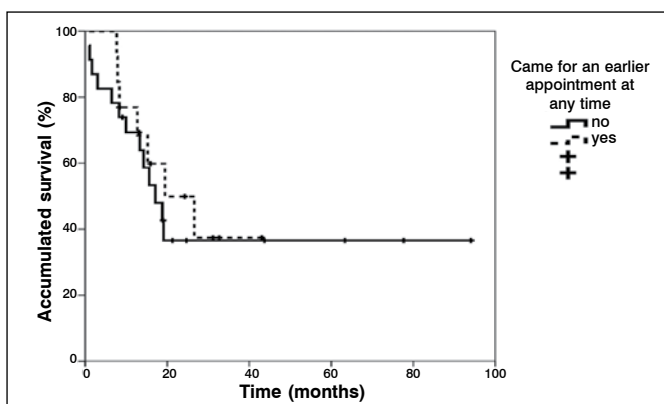
**Figure 1.** Accumulated global survival of patients treated for osteosarcoma.

Source: Pediatric Department, Hospital de Câncer de Barretos.



**Figure 2.** Disease-free survival of patients treated for osteosarcoma.

Source: Pediatric Department, Hospital de Câncer de Barretos.



**Figure 3.** Disease-free survival of patients treated for osteosarcoma, stratified according to early appointment attendance.

Source: Pediatric Department, Hospital de Câncer de Barretos.

As described previously with regards to the rarity of osteosarcoma, the limitation of the casuistry is explicit, in spite of the fact that the study was developed in one of the centers with the highest rates of OS in the country. Some of the main hypotheses for the expressiveness at HCB in relation to the number of patients enrolled in the trial are the reference of the orthopedic

oncology team, easy access to the scheduling of new cases and the prevention program established by HCB, which reaches faraway states, such as Rondônia, which is the state with the second highest patient origin percentages in the study.

According to an analysis carried out by Camargo et al.<sup>10</sup> the incidence of osteosarcoma remains higher in the state of São Paulo, as cited previously, by Parkin et al.<sup>9</sup>, and also confirmed by this study. However, the ideal model would be the multicenter trial, which would validate all the results found.

There are various national studies related to osteosarcoma (treatment, recurrence, results of the Brazilian Cooperative Group), but not exclusively geared towards the follow-up of osteosarcoma, from the point of view of a single institution, as in the present study.

One of the main studies is that of Castro et al.<sup>15</sup>, which gives an account of the experience of the pediatric oncology service of Santa Casa de Misericórdia de São Paulo with osteosarcoma. The objective of this study was to describe the clinical laboratorial characteristics of 60 cases of children and adolescents with osteosarcoma, determining the rates of event-free survival and of global survival. The results were similar to those of this study and of international medical literature, and the authors also reached the conclusion that an early diagnosis in addition to further studies to improve handling and treatment geared towards improvement of quality of life are both essential. International medical literature explains that adolescents are the most affected and that this disease is more common in the second decade of life, i.e., individuals in their twenties.<sup>16</sup>

It is known that, nowadays, the cure is not focused on the disease alone, but also on quality of life after treatment, even though this is related to the late effects of the initial therapy. Accordingly, the development of appropriate long-term follow-up strategies for cancer survivors is becoming more and more necessary.<sup>17</sup> There are numerous US and European studies related to quality of life of the osteosarcoma survivor, through various types of evaluation. In the study by Renard et al.<sup>18</sup> a scoring system of the Musculoskeletal Tumor Society was used to demonstrate better function of the lower limbs in patients who had undergone conservative surgery, instead of amputation.<sup>18</sup> However, other researchers did not find any differences in the result between these two groups, as is the case of Nagarajan et al.<sup>19</sup>, who did not find any differences of functional result in 528 patients from the Childhood Cancer Survivor Study, using the TESS (Toronto Extremity Salvage Score) scale.

This scale consists of a self-applicable questionnaire, with 30 questions assessing performing in daily activities, where a high score corresponds to a high functional level.<sup>20</sup>

The ideal treatment for osteosarcoma is polychemotherapy and surgery, since when relapse occurs, recovery is limited and the survival is very poor, as low as 20%, depending on the type of relapse, the majority of which are pulmonary.<sup>21</sup> It is known that the treatment of pulmonary relapse should be imperative when possible, since the survival of patients with resection of pulmonary metastases is very expressive, as shown by Bacci et al.,<sup>22</sup> who evaluated 235 patients with relapse after neoadjuvant therapy; among the patients treated with surgery, a cure was achieved in 25% of the sample. Continuing with this study, Briccoli et al.<sup>23</sup> reaffirmed the data with 323 patients with osteosarcoma, concluding that in the patients with resectable pulmonary disease

treated with adjuvant and neoadjuvant chemotherapy, thoracotomy should always be considered, regardless of the number of previous resections.

Approximately 50% of OS recurrences occurred within 18 months after the end of therapy and only 5% developed recurrences after five years. Ferrari et al.<sup>24</sup> sought to identify predictive factors in the late relapse of non-metastatic osteosarcoma. The study was carried out over a period of 14 years, at the Rizzoli Institute, comparing 2 groups of patients: those with late relapse (>4 years of follow-up) and those with early relapse. Late relapse was detected in 3.7% of 648 patients from the study. Complete surgical resection was accomplished in 79% of these patients with late relapse and post-relapse survival was 65%, compared with the 20% of survival in the patients with early relapse. LDH, type of surgery and histological response did not significantly differ between the patients with early and late relapse. No clinical predictive factors of late relapse were identified, thus a prolonged follow-up is recommended for all the patients. In another two large series, the most common sites of the disease were: lung (65.8%), bone (8-10%), local (4-7%) and combined (10-15%), also concluding that the control of recurrent OS depends on the complete surgical resection of the affected site. If surgery is not possible, progression and death are certain. Therefore, the most important prognostic factor in the first relapse is complete resection, with a survival rate, at five years, of 20 to 45% for pulmonary metastases and of 20% for other sites. In this sample, pulmonary recurrence was also more frequent, yet without access to the data on resectability and continuity of treatment, since the study ends at the time of recurrence.<sup>24</sup>

What is more challenging in the detection of recurrence is not the diagnosis in symptomatic patients, as these visited the hospital before the scheduled date, when necessary, but instead, asymptomatic patients diagnosed with recurrence in the routine appointment and symptomatic patients who for some reason did not seek medical care at an early stage. There is a high proportion of those who did not reschedule an appointment for an earlier date and presented recurrence, in a ratio of almost 2:1. Thus the conclusion is that it is necessary to take complaints from the patient and their family seriously, always bringing appointments forward when the complaints are pertinent. Therefore, further studies are necessary to detect the real motive of those who presented recurrence, had no complaints and did not reschedule the appointment for an earlier date; and those who presented recurrence, had complaints and did not arrange for an earlier appointment.

Several factors are apparently involved in the delay of the diagnosis and some of them continue to be involved during follow-up, such as distance to the specialized center, transportation and lodging conditions, besides availability for patient examinations. In the patients from the studied sample, it was verified that of those who postponed their appointment, the majority depended on lodgings. In view of this information, it is being discussed whether the postponements occurred due to delay in the release of the funds allocated to traveling costs by the Treatment Outside the Home – TOH system, which can result from delay of medical report, or due to incomplete reports or shortage of public funds for care provision. It could also occur as a result of the postponement of the examination by the Radiology Department due to breakage of apparatus or any

other cause. The only certainty is related to the accommodation vacancy, since no patient belonging to the service attends an appointment late for this reason, as when there are no vacancies, the service is responsible for the allocation for patients. Discussing these hypotheses, it is necessary to know the real role of the TOH. This body, created by Administrative Ruling no. 55, of the Department of Health Care (Ministry of Health), constitutes the legal instrument that ensures, through SUS (Unified Health System), that medical treatment is provided to patients with diseases that are untreatable in the municipality of origin, due to lack of technical conditions.<sup>25</sup>

It is observed that the use of TOH resources is subject to an extensive bureaucratic process that depends on several factors, especially on the familiarity of the physician from that body with pediatric oncology, as this individual is responsible for evaluating the need for adequate post-treatment follow-up.

The second discussion concerns the purchasing power of each state, as it is no use patients having the right to receive treatment outside their place of abode if the state does not have funds to provide the medical care. Due to the vastness of our country, there are places that do not have minimum levels of access to health, to culture or any other information, because social exclusion also exists in south and southeast Brazil, thus complicating the post-treatment follow-up program, confirming what was revealed in the study, i.e., that distance does not constitute the only cause of late attendance of appointments. There are no patients either at HCB, or rather, in this study, who come from one of the 10 cities classified as the poorest in the country, evaluated by the social exclusion index (SEI), although there are states of origin such as the state of Piauí, located north of the Tropic of Capricorn, which suffers even more with social exclusion.

The SEI data reveal that 2,290 Brazilian cities, equivalent to 42% of the total municipalities, which contain 21% of the country's population, exhibit high rates of social exclusion. On the other hand, only 200 cities (3.6% of the total), present an adequate standard of living.<sup>26</sup> More than 25% of Brazilians live in precarious conditions, with a low income, without formal employment and with limited access to education. According to the SEI, the data reveal that a historical scenario of exclusion appears to be firmly established in the north and northeast regions, hindering the follow-up and adequate treatment of cancer in general.

The third discussion is related to the postponement of the radiological examinations, where the medical team often becomes aware of the situation only when they detect the patient's absence at the scheduled appointment. A backup mechanism should be created for this solution, since many asymptomatic patients, without evidence of urgency, can be jeopardized due to failure in early detection of recurrence. As regards the symptomatic patients, who arrive at the hospital and need to have urgent exams, but cannot wait for the maintenance of radiology equipment, it is a philosophy of HCB to consider them a top priority, performing the necessary examination anyhow.

Having covered the social and operational points, which may interfere in the delay of the recurrence diagnosis, it is known that the early examination of pulmonary recurrence will interfere mainly in the quality of life of the patient, since as it is resectable, there is an improvement in the survival quality, although not in a statistically significant manner, as seen in this study, where the recurrence-free survival was no different from those

that presented recurrence and did not come for an appointment earlier than the original date.

This means that further molecular studies are necessary for us to increasingly manage to obtain a detailed patient profile, as is the case of tumor activity markers, which can interfere in the response to treatment and in relapse, allowing an investment in new multicenter studies for the discovery of new drugs and new markers. Faced with the difficulty of response in patients presenting recurrence, Zhao et al.<sup>27</sup> published a study that assessed the efficacy of pirarubicin in association with chemotherapy in patients with pulmonary metastases. That study evaluated the effect and adverse reactions of pirarubicin (THF) in association with cisplatin or ifosfamide and analyzed the relation between therapeutic effect and the expression of P-glycoprotein and topoisomerase-II. There was no difference in the global survival and in the progression-free survival between the use of cisplatin and ifosfamide, but it had an effect on the negativation of P-glycoprotein and/or topoisomerase-II. Therefore, for patients with pulmonary relapse, THF in association with chemotherapy was effective.<sup>27</sup>

It is indisputable that the follow-up of cancer patients is necessary, yet the form and frequency give rise to doubt. Several formulas were developed in the attempt to discover the best follow-up, such as the Collins formula, which, however, does not apply to all types of tumor, including OS.<sup>28</sup> There is no

consensus regarding a follow-up plan for OS, and authors only agree on its importance.<sup>4</sup>

Therefore, in view of the urgent need for follow-up of patients treated for OS, several aspects still need to be studied in depth, such as the cost and effectiveness of childhood cancer treatment, and consequently, of the post-treatment program and even of the palliative care. It is known that the economic weight of cancer is substantial, yet it is possible to estimate direct and indirect costs for a large number of cancer patients, using databases related to the sociodemographic, demographic, and geographical characteristics, besides those of the type that would improve research and the quality of treatment, of follow-up and even of the act of dying.<sup>29</sup>

## CONCLUSION

Hence it is concluded that the complaint observed in the appointments is associated with the positive test result, without any association between the demographic and clinical characteristics with regard to early appointment attendance. The patients who did not present recurrences took longer to schedule an appointment than those presenting recurrence. The evaluation showed a statistically significant association between the patients who brought any appointment forward and those who had complaints. In the appointments with cases of late attendance, 54.5% of the patients were staying at lodgings.

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