

## Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: Prognostic Factors and Impact on Survival

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### A B S T R A C T

#### Purpose

To evaluate the impact of chemotherapy and surgery on the outcome of osteosarcoma (OS) of the extremities and to identify prognostic factors in Brazilian patients.

#### Patients and Methods

A total of 225 patients with metastatic and nonmetastatic OS of the extremities were enrolled and assessed in two consecutive studies designed and implemented by the Brazilian Osteosarcoma Treatment Group.

#### Results

The 5-year survival and event-free survival rates for the 209 assessable patients were 50.1% and 39%, respectively; for the 178 patients with nonmetastatic disease at diagnosis, the rates were 60.5% and 45.5%, respectively. The multivariate analysis showed that the following variables were associated with a shorter survival: metastases at diagnosis ( $P < .001$ ), necrosis grades 1 and 2 ( $P = .046$ ), and tumor size ( $P = .0071$ ).

#### Conclusion

The overall 5- and 10-year survival rates were lower than the rates reported in North American and European trials. A pattern of advanced disease at diagnosis was often present, with a high proportion of patients having metastases (20.8%) and large tumor size (42.9%). However, these features were not necessarily associated with longer duration of prediagnostic symptoms. These findings were considered in the strategic planning of the current Brazilian cooperative study, with the aim of improving survival and quality of life of a large number of patients with OS.

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### INTRODUCTION

The efficacy of chemotherapy and its impact on the survival of osteosarcoma (OS) patients is well documented, and therapeutic trials conducted by North American and European centers and groups have resulted in 5-year survival rates between 50% and 75%.<sup>1-8</sup> However, patients who are part of the two thirds of the world population living in developing countries have not benefited from these successful results. Actually, little information is currently available about tumor features and treatment results in this population.<sup>9,10</sup> In Brazil, where the total population is 169 million people, of whom 49 million are less than 15 years of age and 16 million are between 15 and 19 years old, 350 new cases of OS are estimated to be diagnosed each year.<sup>11</sup>

The objectives of the Brazilian Osteosarcoma Treatment Group (BOTG) are to obtain detailed information on the clinical features, outcome, and epidemiology of OS in Brazil to help develop new treatment strategies, considering local conditions. Four consecutive studies have been completed by the group. Study I started in 1982 and resulted in a 3-year event-free survival (EFS) rate of 44.1%.<sup>9</sup> Study II was conducted between 1987 and 1990 and showed 3-year EFS rate of 65%, identifying tumor size, grade of necrosis, and type of surgery as relevant prognostic factors.<sup>10</sup>

Study III, which was started in 1991 and closed in 1996, had the following two main objectives: (1) limiting the use of high-dose methotrexate (MTX) in patients considered to have a worse prognosis, and (2) to determine the activity of two cycles of intra-arterial carboplatin as a single agent

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administered up front to a limited number of patients. Study IV was conducted from 1996 to 1999 with the major purpose of intensifying chemotherapy by using two platinum compounds (carboplatin and cisplatin) in combination with doxorubicin and ifosfamide administered after surgery. In total, 225 patients were enrolled onto studies III and IV, and to the best of our knowledge, this represents the largest OS survey conducted by a cooperative group in a developing country. Studies III and IV are the object of this report.

## PATIENTS AND METHODS

### Enrollment

Two hundred twenty-five patients younger than 25 years of age with high-grade OS of the extremities (metastatic and nonmetastatic) were prospectively enrolled onto the BOTG studies III and IV. The following five institutions enrolled patients: Instituto de Oncologia Pediatrica, GRAACC/UNIFESP (Grupo de Apoio ao Adolescente e à Criança com Câncer/Universidade Federal de São Paulo; n = 144); Hospital do Câncer (n = 36); Hospital das Clínicas-FMUSP (Faculdade de Medicina da Universidade de São Paulo; n = 19); Santa de Casa de Misericórdia in São Paulo (n = 15); and Hospital de Clínicas in Porto Alegre (n = 11). The studies were previously approved by the research ethics committees of each institution, and informed consent was obtained from the patients or their legal representatives.

### Diagnostic Staging and Treatment

After histologic confirmation of high-grade OS, an initial evaluation was performed, consisting of complete medical history and physical examination, CBC, and full biochemistry, including alkaline phosphatase, lactic dehydrogenase, and electrolytes. Eligible patients were required to have normal renal (blood urea nitrogen, creatinine, and creatinine clearance), hepatic (AST, ALT, bilirubin, and coagulation profile), and cardiac functions (echocardiogram and ECG) for age.

Normal audiometric evaluation at diagnosis was also required for patients to be enrolled onto study IV. Radiographic assessments at diagnosis included plain chest x-ray, computed tomography of the chest, radioisotope bone scan, and a computed tomography scan or magnetic resonance imaging of the affected bone. These assessments were repeated at the end of the preoperative therapy and at regular intervals thereafter, during and after the end of therapy, for at least 5 years and then twice a year.

In study III, chemotherapy (regimen A) consisted of epirubicin (75 mg/m<sup>2</sup> short-term intravenous [IV] infusion on day 1 of weeks 0, 6, 11, 17, 20, and 23), carboplatin (600 mg/m<sup>2</sup> IV on day 1 of weeks 3, 6, 14, and 17), and ifosfamide 3 g/m<sup>2</sup> and mesna on days 1, 2, and 3 of weeks 0, 3, 11, 14, 20, and 23 (Fig 1). Thirty-three patients received two cycles of intra-arterial carboplatin as a single agent up front.<sup>12</sup> Patients requiring amputation or presenting with large tumors (> 12 cm) were considered to be at high risk of treatment

failure, and MTX 12 g/m<sup>2</sup> was added on weeks 11, 12, 19, 20, 27, and 28 (regimen B; Fig 1).

In study IV, patients received carboplatin (500 mg/m<sup>2</sup> IV on day 1 of weeks 0, 3, 6, 17, and 26) and cisplatin (100 mg/m<sup>2</sup> IV on day 1 of weeks 0, 3, 6, 11, and 20). Doxorubicin was administered either at a dose of 30 mg/m<sup>2</sup> in short-term IV infusions on days 1 and 2 of weeks 0, 3, 6, 14, 17, and 23 in the initial phase of the study or at a dose of 35 mg/m<sup>2</sup> following the same schedule as administered in a previous group with dexrazoxane. Ifosfamide 3 g/m<sup>2</sup> and mesna IV on days 1, 2, and 3 were added on weeks 11, 14, 20, and 26 (Fig 2).

The appropriate surgical procedure for each patient was determined by the orthopedics team in collaboration with the pediatric oncology team. Non-conventional endoprosthesis, resection of expendable bones, plaques, and bone graft fixation (autograft or bone bank) have been used. All pulmonary metastases were surgically removed, whenever possible, after resection of the primary tumor.

### Assessment of Patients and Tumor- and Treatment-Related Variables

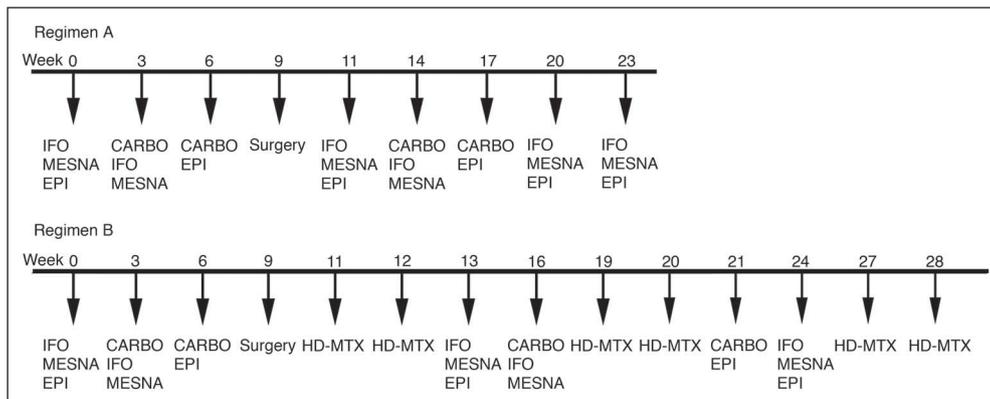
The following variables were evaluated: treatment schedule, sex, age at enrollment, time from onset of symptoms to diagnosis, primary tumor site, presence or absence of metastases at diagnosis, tumor size ( $\leq 12$  cm or  $> 12$  cm), type of surgery (conservative or amputation), and histologic response.

Response to preoperative chemotherapy was determined by the grade of necrosis, as defined by Huvos<sup>13</sup> as follows: grade 1, less than 50% tumor necrosis; grade 2, 50% to 90% tumor necrosis; grade 3, more than 90% tumor necrosis; and grade 4, 100% necrosis. Patients with nonmetastatic disease were considered to be in complete remission on the date of the primary tumor resection, and patients with metastatic tumors were considered to be in complete remission on the date of the pulmonary metastases resection. Relapses were divided into the following two categories: early relapse (< 1 year after the end of chemotherapy) and late relapse (> 1 year after completion of chemotherapy).

### Statistical Analysis

Patients were evaluated with respect to their tumor characteristics, and these variables were correlated with survival. Overall survival was defined as the time interval between the date of enrollment onto the study and death from any cause, including secondary malignancies, or the most recent follow-up contact. EFS was defined as the time interval between enrollment onto the study and disease relapse, death from any cause, or the most recent follow-up contact. All qualitative variables were evaluated using the  $\chi^2$  test or the Fisher's exact test, when necessary, to check for possible associations between patient and tumor characteristics.

The overall survival and EFS curves were created using the Kaplan-Meier method, and log-rank tests were used to compare the curves. The characteristics evaluated by univariate analysis were used as explanatory variables in the Cox regression models of survival and EFS and final multivariate models; significant effects at 5% were reported.



**Fig 1.** Protocol design for study III. IFO, ifosfamide; EPI, epirubicin; CARBO, carboplatin; HD-MTX, high-dose methotrexate.

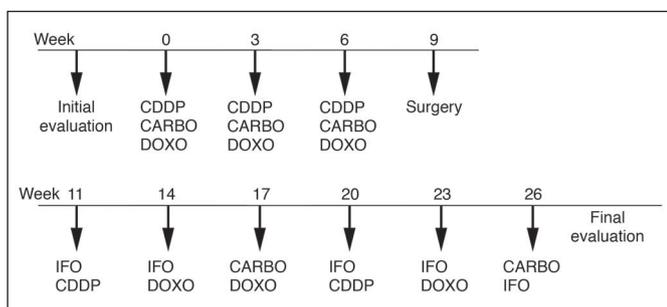


Fig 2. Protocol design for study IV. CDDP, cisplatin; CARBO, carboplatin; DOXO, doxorubicin; IFO, ifosfamide.

RESULTS

Distribution of Demographics and Tumor-Related Variables

Two hundred twenty-five patients with high-grade OS of the extremities were enrolled onto studies III (105 patients) and IV (120 patients). Sixteen (7.2%) patients were considered not assessable because of discontinuation of treatment (n = 6), surgery refusal (n = 9), and nonresectable tumor (n = 1). Two hundred nine patients were evaluated for survival and EFS.

However, the whole population of 225 patients was used for describing demographic data (Table 1) and was included in the intent-to-treat analysis. The male to female ratio was 1.4, and the mean age at diagnosis was 14.0 ± 4.1 years (range, 2.4 to 24.5 years). The mean time from onset of symptoms to diagnosis was 129 days (range, 2 to 1,058 days; median, 90 days).

The most frequent primary tumor sites are listed on Table 1. Forty-seven patients (20.9%) had metastatic disease at diagnosis, and of these, 37 (78.7%) had pulmonary metastases, four (8.5%) had bone metastases, and six (12.8%) had simultaneous bone and pulmonary metastases.

Surgical Treatment

Seven (3.3%) of the 209 assessable patients died before surgery; four died as a result of chemotherapy-related toxicity, and three died as a result of disease progression. Sixty-nine patients (33%) underwent amputation, and 133 patients (63.6%) underwent conservative surgery (Table 2). Of these 133 patients, 97 (72.9%) received endoprosthesis, 28 (21.1%) had tumor resection followed by replacement with bone graft and osteosynthesis with plates, and eight (6%) had simple resection.

Eighteen patients (8.6%) underwent amputation before chemotherapy because of the size of the tumor. Local relapse occurred in 21 patients (10%), and of these patients, 19 underwent conservative surgery (14 endoprostheses, two bone graft surgeries, and three resections).

All but two of the patients with local relapse had tumor-free margins, but 11 (8.9%) of 124 assessable specimens presented inadequate margins after conservative surgery. Eight of the patients with local relapse subsequently underwent amputation. The overall proportion of amputations in studies III and IV combined was 38.1%. Patients without metastases at diagnosis had the majority (P = .027) of conservative surgeries compared with patients with metastases at diagnosis (69.3% v 50%, respectively).

Histologic Response to Preoperative Chemotherapy

One hundred ninety-four patients had either conservative surgery or amputation after chemotherapy, and the histologic response was determined in 160 patients (Table 2). The proportion of good responders (necrosis grades 3 and 4) in the two studies combined was 29.4%, and the proportion of poor responders (necrosis grades 1 and 2) was 70.6%. The proportion of patients achieving grade 3 or 4 necrosis in study III (46.9%) was higher than that proportion obtained in study IV (17.7%; P < .001). There was no significant difference in the histologic response distribution between patients with metastatic and patients with nonmetastatic disease at diagnosis (P = .928). No association was found between the tumor size and histologic response (P = .516).

Table 1. Demographic Characteristics of Enrolled Patients With Osteosarcoma of the Extremities (N = 225)

Characteristic	Metastases at Diagnosis				Total (N = 225)		P
	Yes (n = 47; 20.9%)		No (n = 178; 79.1%)		No.	%	
	No.	%	No.	%			
Study							
III	22	46.8	83	46.6	105	46.7	.983
IV	25	53.2	95	53.4	120	53.3	
Sex							
Male	27	57.4	104	58.4	131	58.2	.904
Female	20	42.6	74	41.6	94	41.8	
Age							
≤ 14 years	21	44.7	90	50.6	111	49.3	.473
> 14 years	26	55.3	88	49.4	114	50.7	
Primary tumor site							
Femur	31	66.0	96	53.9	127	56.4	.053
Tibia	9	19.1	58	32.6	67	29.8	
Humerus	3	6.4	18	10.1	21	9.3	
Fibula	4	8.5	2	1.1	6	2.7	
Others	0	0.0	4	2.3	4	1.7	

**Table 2.** Tumor Features and Therapy Results by Study

Factor	Study						P
	III		IV		Total		
	No.	%	No.	%	No.	%	
Type of surgery, n = 202							
Amputation	37	40.2	32	29.1	69	34.2	.097
Conservative	55	59.8	78	70.9	133	65.8	
Histologic response, grade of necrosis, n = 160							
Grade 1	21	32.8	37	38.5	58	36.2	.001
Grade 2	13	20.3	42	43.8	55	34.4	
Grade 3	20	31.3	11	11.5	31	19.4	
Grade 4	10	15.6	6	6.3	16	10.0	
Tumor size, n = 184							
≤ 12 cm	44	51.8	61	61.6	105	57.1	.178
> 12 cm	41	48.2	38	38.4	79	42.9	

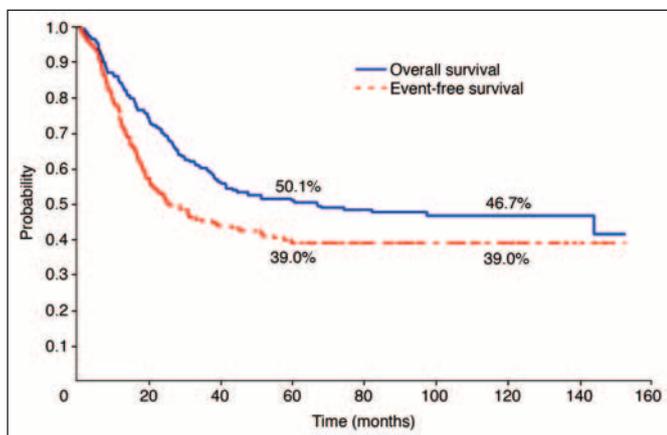
### Overall Survival and EFS

The mean follow-up time was 61 months (range, 1.4 to 152.7 months). Among the 209 patients analyzed, 98 were alive at the time of the analysis, 110 had died, and one had been lost to follow-up. The causes of death were as follows: disease relapse, 74 patients (67.3%); disease progression, 18 patients (16.4%); chemotherapy toxicity, 15 patients (13.6%); second neoplasia, one patient (0.9%); and other causes, two patients (1.8%). The overall incidence of toxicity-related death was 7.2% (15 of 209 patients), and 12 (80%) of 15 patients died from neutropenia and septic shock in study IV. The disease progression rate was 8.6% (18 of 209 patients).

Ninety-two patients (44.0%) experienced disease relapse or disease progression. The mean time to relapse was 19.7 months, and the lungs were the most frequent site of relapse. Twenty patients (30.4%) developed early relapse. The longest time to relapse was 59.7 months. Patients with metastases at diagnosis tended to relapse earlier, at an average of 12.9 months. Seventeen of the relapsing patients (18.5%) were rescued; however, none of the patients with metastases at diagnosis who relapsed survived. The estimated 5- and 10-year survival rates for all patients were 50.1% and 46.7%, respectively. The EFS rate was 39.0% at both 5 and 10 years (Table 3, Fig 3). The estimated 5- and 10-year survival rates for the nonmetastatic patients were 60.5% and

**Table 3.** Univariate Analysis of Overall and Event-Free Survival Based on Kaplan-Meier Estimates of Survival Curves and Log-Rank Tests for All Assessable Patients

Factor	No. of Patients	Overall Survival					Event-Free Survival				
		5 Years		10 Years		P (log-rank)	5 Years		10 Years		P (log-rank)
		%	SE (%)	%	SE (%)		%	SE (%)	%	SE (%)	
Overall Study	209	50.1	3.5	46.7	3.6		39.0	3.4	39.0	3.4	
III	96	54.2	5.1	50.0	5.1	.514	39.6	5.0	39.6	5.0	.842
IV	113	48.3	4.7	43.5	5.1		38.4	4.6	38.4	4.6	
Metastases at diagnosis											
Yes	41	12.2	5.1	12.2	5.1	< .001	12.2	5.1	12.2	5.1	< .001
No	168	60.5	3.8	55.2	4.0		45.5	3.9	45.5	3.9	
Type of surgery											
Amputation	69	37.7	5.8	34.0	5.9	< .001	30.4	5.5	30.4	5.5	.004
Conservative	133	60.6	4.3	56.0	4.4		45.5	4.3	45.5	4.3	
Tumor size											
≤ 12 cm	105	64.5	4.7	59.8	4.9	< .001	48.1	4.9	48.1	4.9	.009
> 12 cm	79	40.5	5.5	35.5	5.6		30.4	5.2	30.4	5.2	
Histologic response, grade of necrosis											
Grade 1	58	44.8	6.5	36.8	6.5	.005	31.0	6.1	31.0	6.1	.005
Grade 2	55	48.2	6.8	45.8	6.8		31.5	6.3	31.5	6.3	
Grade 3	31	77.4	7.5	73.9	7.8		64.5	8.6	64.5	8.6	
Grade 4	16	68.8	11.6	68.8	11.6		62.5	12.1	62.5	12.1	
Primary tumor											
Femur	120	46.3	4.6	41.8	4.7	.232	36.6	4.3	36.6	4.3	.180
Tibia	65	60.0	6.1	56.7	6.2		49.2	6.2	49.2	6.2	
Humerus	16	50.0	12.5	43.8	12.4		37.5	12.1	37.5	12.1	
Others	8	50.0	17.7	50.0	17.7		37.5	17.1	37.5	17.1	



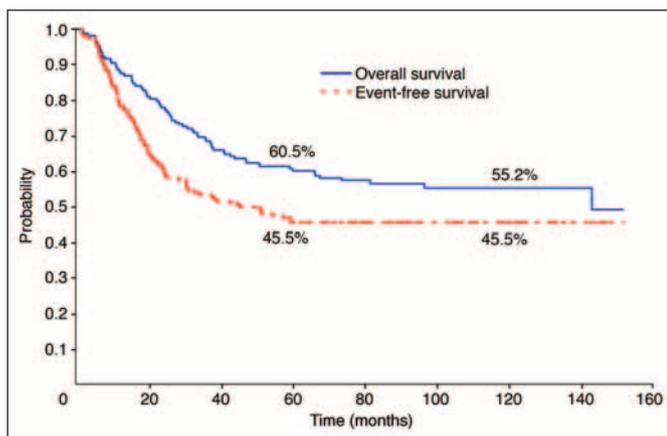
**Fig 3.** Overall and event-free survival of osteosarcoma patients with primary tumor of the extremity (209 patients).

55.2%, respectively, and the EFS rate was 45.5% at both 5 and 10 years (Fig 4). For the metastatic patients, the 5- and 10-year overall survival and EFS rates were all 12.2% (Table 3, Fig 5A).

The analysis of prediagnostic symptom duration did not reveal any statistically significant correlation with tumor size ( $P = .865$ ), presence of metastases ( $P = .678$ ), or survival and EFS rates. Tumor size was associated with the presence of metastases ( $P = .023$ ).

The characteristics that significantly correlated with survival and EFS were metastases at diagnosis, type of surgery, tumor size, and grade of necrosis (Table 3, Figs 5A to 5D). The multivariate analysis for independent prognostic factors is presented in Table 4.

Forty-five patients in study III received regimen B, and the 5- and 10-year overall survival rates for patients not receiving MTX were 62.8% and 60.8%, respectively, whereas the 5- and 10-year survival rates for patients receiving MTX were 44.4% and 37.8%, respectively ( $P = .017$ ). The intent-to-treat analysis including all of the 225 patients enrolled onto the two studies demonstrated 5- and 10-year overall survival rates of 47.3% and 43.3%, respectively. Patients without metastases at diagnosis had 5- and 10-year overall survival rates of 57.1% and 52.0%, respectively, whereas the 5- and 10-year survival rates for patients with metastatic disease were both 10.6% (Fig 6).



**Fig 4.** Overall and event-free survival of osteosarcoma patients with primary tumor of the extremity who were nonmetastatic at diagnosis (168 patients).

## DISCUSSION

These two consecutive BOTG studies have shown that nearly half of these OS patients can be cured if they receive appropriate treatment.<sup>14</sup> The outcome of these Brazilian trials is still below the 70% to 75% 5-year survival rates in nonmetastatic patients reported by European and North American authors.<sup>4,5,7,8</sup>

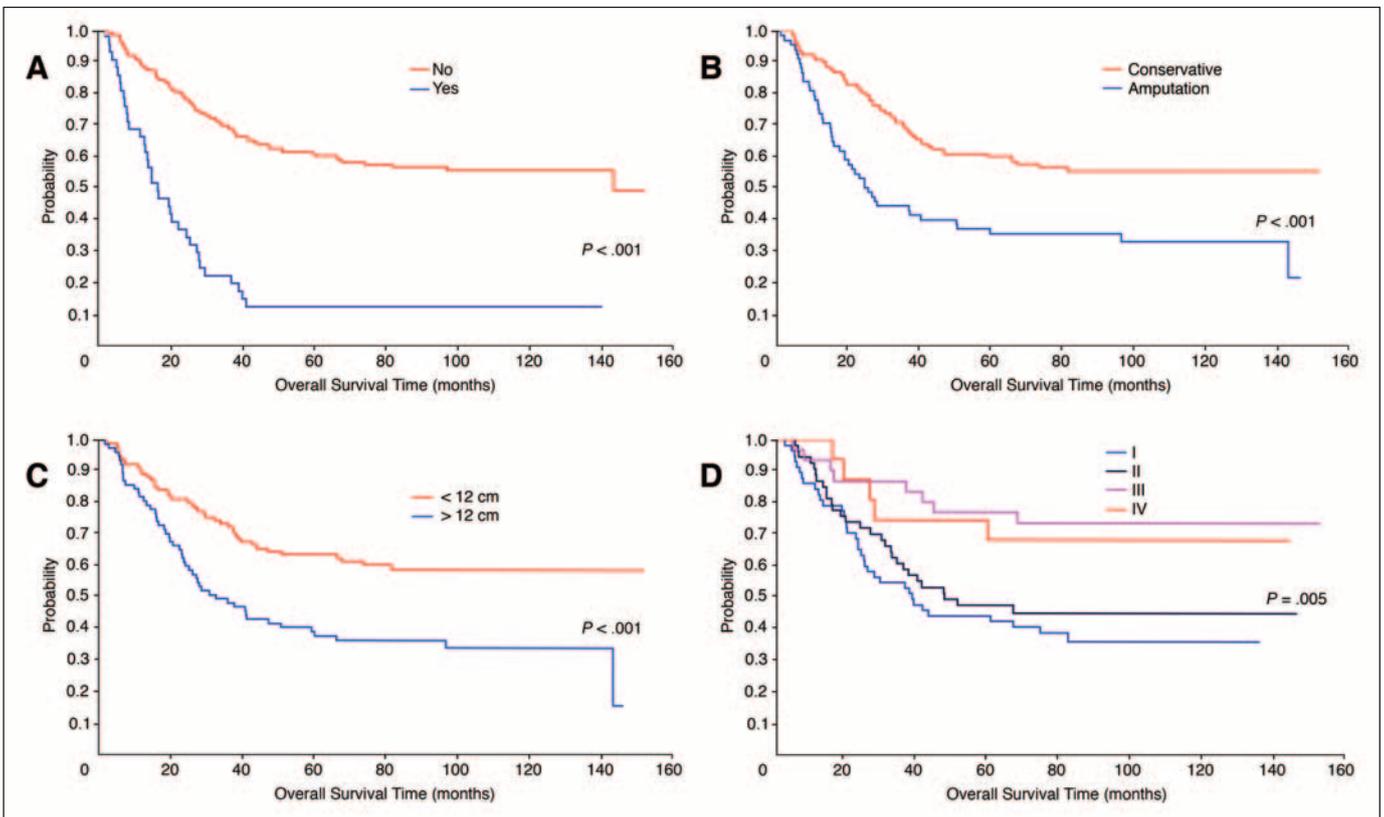
The number of patients included in the two studies (ie, 30 per year) represents 10% of the expected number of OS patients in Brazil, revealing that, with some exceptions, most of these patients are not receiving adequate treatment. Several factors previously identified to be of significant prognostic influence were confirmed in the Brazilian population, including the presence of metastases at diagnosis, tumor size, primary site, grade of postchemotherapy histologic necrosis, and surgical resectability.<sup>15-23</sup>

Metastases at diagnosis were present in 21% of our patients, which is higher than the frequency reported by other investigators.<sup>7,8,16,20,23</sup> This finding reflects the frequency of advanced disease at diagnosis among our patient population. However, we were unable to document whether this finding was secondary to the delay in establishing diagnosis. Surprisingly, the time from onset of symptoms to diagnosis did not correlate with the presence of metastases, tumor size, or survival. These data suggest that the stage of disease at presentation depends more on biologic properties of the tumor than on late diagnosis. Bacci et al<sup>24</sup> reported primary tumor spread to be associated with shorter prediagnostic symptom duration and hypothesized that this could be related to a more aggressive biologic behavior. Bielack et al<sup>7</sup> reported 69 days (range, 1 day to 5 years and 8 months) as the median of onset of symptoms to diagnosis. These variables showed a positive correlation with tumor size and presence of metastases at diagnosis, but they were not prognostic factors for survival or EFS. In our studies, the presence of metastases at diagnosis was identified as the most significant single factor influencing outcome, and the patients with metastases at diagnosis had a dismal 10-year survival and EFS rate of 12%.

Patients with metastatic disease more often presented with large tumors, and they required amputation at a significantly higher rate than patients with small-sized tumors. The multivariate analysis has shown that the presence of metastases, tumor size more than 12 cm, and necrosis grades 1 and 2 were independent prognostic factors that significantly decreased survival time.

Although reports from phase II studies performed in advanced or metastatic OS patients suggest that carboplatin may be less active than cisplatin,<sup>25,26</sup> the difference in distribution of grade of necrosis between studies III and IV may have resulted from the administration of intra-arterial carboplatin in study III. The group of 33 patients who received intra-arterial carboplatin up front as a single agent had a favorable clinical and radiologic response.<sup>12</sup> Bacci et al,<sup>27</sup> who used IV cisplatin in association with MTX and doxorubicin, demonstrated a response rate of 46%. However, with the intra-arterial administration of cisplatin, the response rate was increased to 77%, suggesting improved efficacy when administered this way.<sup>12,28</sup> In a controlled trial, Winkler et al<sup>29</sup> showed no enhancement of the antitumoral effect of cisplatin when comparing intra-arterial and IV administration.

In study III, patients receiving regimen A achieved significantly higher survival rates compared with patients receiving regimen B, suggesting that the isolated addition of high-dose MTX did not

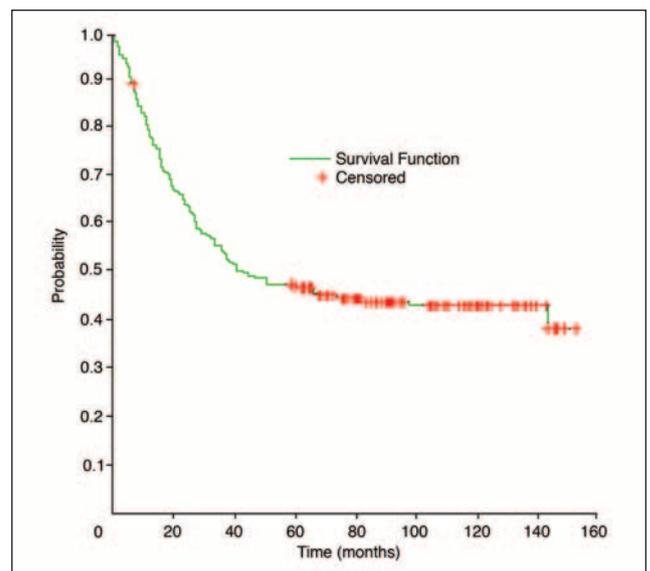


**Fig 5.** Overall survival curves for assessable patients with osteosarcoma of the extremities by prognostic factors. (A) Metastases at diagnosis; (B) type of surgery; (C) tumor size; (D) histologic response—grade of necrosis.

improve outcome of these patients with poor prognosis. In study IV, three drugs were used in the preoperative phase, and the proportion of good responders was inferior to study III, showing that the intensification of platinum derivatives did not improve the grade of necrosis or the survival rate but increased the incidence of toxicity-related death. The increased rate of conservative surgery from 59.8% on study III to 70.9% on study IV, despite a better rate of good response in study III, was a relevant finding. Because the patient characteristics were comparable, we believe that the decrease in the number of amputations can be partly explained by the advances in orthopedic surgery. However, it should be noted that 14.3% of patients developed local relapse after

conservative surgery. The fact that, in Brazil, amputation is not easily accepted, especially of upper extremities, may have influenced the decision of some orthopedic surgeons to perform procedures associated with greater risk of recurrence. Italian investigators<sup>30</sup> have reported the best limb-preservation rate, and they attribute these results

Table 4. Prognostic Factors in Final Cox Regression Models for Survival and Event-Free Survival			
Model	P	Relative Risk	95% CI for Relative Risk
Overall survival final model			
Metastases: yes	< .001	3.016	1.72 to 5.288
Tumor size: > 12 cm	.007	1.931	1.199 to 3.112
Grade of necrosis: 1-2	.001	3.15	1.608 to 6.174
Event-free survival final model			
Metastases: yes	.001	2.617	1.522 to 4.501
Tumor size: > 12 cm	.039	1.578	1.022 to 2.437
Grade of necrosis: 1-2	.001	2.775	1.56 to 4.935



**Fig 6.** Intent-to-treat analysis (N = 225).

to the centralization of orthopedic surgeries.<sup>31,32</sup> Our data demonstrated that the lungs were the most common site of recurrence, with an incidence identical to that reported by Bacci et al,<sup>30</sup> Meyers et al,<sup>8</sup> and Goorin et al.<sup>22</sup>

Evaluation of the time to relapse showed that patients with metastatic disease relapsed earlier, and none of them survived. However, 18.5% of patients with nonmetastatic disease who experienced relapse achieved a new complete remission.

The results of studies III and IV have shown that our OS patient population often presents with advanced disease, as demonstrated by the high incidence of metastasis at diagnosis, the large tumors, and the need for amputation. The analysis of prediagnostic symptom duration confirmed that a longer period with symptoms did not correlate with

a worse clinical presentation or outcome, suggesting that biologic factors influence the disease behavior and treatment outcome.

As a result of the favorable experience gathered from the cooperative work, the BOTG has expanded and now comprises 26 centers in Brazil. A center for data collection, tumor pathology revision, tumor tissue banking, molecular biology studies, and surgical and anatomic-pathology protocols has been implemented, offering more favorable conditions to increase the number of Brazilian patients with OS who receive state of the art treatment. Exchange of information between Brazilian and North American investigators has led to the design and implementation of the OS 2000 protocol, which is expected to increase considerably the number of enrolled patients whose outcome will be improved.

## REFERENCES

- Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse free survival in patients with osteosarcoma of extremity. *N Engl J Med* 314:1600-1606, 1986
- Meyers PA, Heller G, Healey J, et al: Chemotherapy for nonmetastatic osteogenic sarcoma: The Memorial Sloan-Kettering experience. *J Clin Oncol* 10:5-15, 1992
- Winkler K, Beron G, Delling G, et al: Neoadjuvant chemotherapy of osteosarcoma: Results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. *J Clin Oncol* 6:329-337, 1988
- Bacci G, Ferrari S, Bertoni F, et al: Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Instituto Ortopedico Rizzoli according to the Instituto Ortopedico Rizzoli/Osteosarcoma-2 protocol: An updated report. *J Clin Oncol* 18:4016-4027, 2000
- Meyers PA, Gorlick R, Heller G, et al: Intensification of Preoperative Chemotherapy for Osteogenic Sarcoma: Results of the Memorial Sloan-Kettering (T12) protocol. *J Clin Oncol* 16:2452-2458, 1998
- Rosen G, Marcove RC, Caparros B, et al: Primary osteogenic sarcoma: The rationale for preoperative chemotherapy and delayed surgery. *Cancer* 43:2163-2177, 1979
- Bielack SS, Kempf-Bielack B, Delling G, et al: Prognostic factors in high-grade osteosarcoma of the extremities or trunk: An analysis of 1,702 patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol* 20:776-790, 2002
- Meyers P, Schwartz C, Krailo M, et al: Osteosarcoma: A randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. *J Clin Oncol* 23:2004-2011, 2005
- Petrilli AS, Gentil FC, Epelman S, et al: Increased survival, limb preservation, and prognostic factors for osteosarcoma. *Cancer* 68:733-737, 1991
- Petrilli AS, Penna Y, Lopes A, et al: IIB osteosarcoma: Current management, local control, and survival statistics—Sao Paulo, Brazil. *Clin Orthop Relat Res* 270:60-66, 1991
- Instituto Brasileiro de Geografia e Estatística: Censo Demográfico 2000. <http://www.ibge.gov.br>
- Petrilli AS, Kechichian R, Broniscer A, et al: Activity of intraarterial carboplatin as a single agent in the treatment of newly diagnosed extremity osteosarcoma. *Med Pediatr Oncol* 33:71-75, 1999
- Huvos AG: Bone Tumors: Diagnosis, Treatment, and Prognosis (ed 2). Philadelphia, PA, Saunders, 1991
- Marina N, Gebhardt M, Teot L, et al: Biology and therapeutic advances for pediatric osteosarcoma. *Oncologist* 9:422-441, 2004
- Bieling P, Rehan N, Winkler P, et al: Tumor size and prognosis in aggressively treated osteosarcoma. *J Clin Oncol* 14:848-858, 1996
- Kager L, Zoubek A, Potechger U, et al: Primary metastatic osteosarcoma: Presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol* 21:2011-2018, 2003
- Rodriguez-Galindo C, Shah N, McCarville MB, et al: Outcome after local recurrence of osteosarcoma: The St. Jude Children's Research Hospital experience (1970-2000). *Cancer* 100:1928-1935, 2004
- Chi SN, Conklin LS, Qin J, et al: The patterns of relapse in osteosarcoma: The Memorial Sloan-Kettering experience. *Pediatr Blood Cancer* 42:46-51, 2004
- Jaffe N, Carrasco H, Raymond K, et al: Can cure in patients with osteosarcoma be achieved exclusively with chemotherapy and abrogation of surgery? *Cancer* 95:2202-2210, 2002
- Meyers PA, Heller G, Healey JH, et al: Osteogenic sarcoma with clinically detectable metastasis at initial presentation. *J Clin Oncol* 11:449-453, 1993
- Bacci G, Ruggieri P, Bertoni F, et al: Local and systemic control for osteosarcoma of the extremity treated with neoadjuvant chemotherapy and limb salvage surgery: The Rizzoli experience. *Oncol Rep* 7:1129-1133, 2000
- Goorin AM, Schwartzentruber DJ, Devidas M, et al: Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. *J Clin Oncol* 21:1574-1580, 2003
- Bacci G, Briccoli A, Rocca M, et al: Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: Recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. *Ann Oncol* 14:1126-1134, 2003
- Bacci G, Ferrari S, Longhi A, et al: High grade osteosarcoma of the extremity: Differences between localized and metastatic tumors at presentation. *J Pediatr Hematol Oncol* 24:27-30, 2002
- Ferguson WS, Harris MB, Goorin AM, et al: Presurgical window of carboplatin and surgery and multidrug chemotherapy for the treatment of newly diagnosed metastatic or unresectable osteosarcoma: Pediatric Oncology Group Trial. *J Pediatr Hematol Oncol* 23:340-348, 2001
- Ettinger LJ, Gaynon PS, Krailo MD, et al: A phase II study of carboplatin in children with recurrent or progressive solid tumors: A report from the Childrens Cancer Group. *Cancer* 74:1297-1301, 1994
- Bacci G, Ferrari S, Tienghi A, et al: A comparison of methods of loco-regional chemotherapy combined with systemic chemotherapy as neoadjuvant treatment of osteosarcoma of the extremity. *Eur J Surg Oncol* 27:98-104, 2001
- Jaffe N, Robertson R, Ayala A, et al: Comparison of intra-arterial cis-diamminedichloroplatinum II with high-dose methotrexate and citrovorum factor rescue in the treatment of primary osteosarcoma. *J Clin Oncol* 3:1101-1104, 1985
- Winkler K, Bielack S, Delling G, et al: Effect of intraarterial versus intravenous cisplatin in addition to systemic doxorubicin, high-dose methotrexate, and ifosfamide on histologic tumor response in osteosarcoma (Study COSS-86). *Cancer* 66:1703-1710, 1990
- Bacci G, Ferrari S, Longhi A, et al: Pattern of relapse in patients with osteosarcoma of the extremities treated with neoadjuvant chemotherapy. *Eur J Cancer* 37:32-38, 2001
- Hosalkar HS, Dormans JP: Limb sparing surgery for pediatric musculoskeletal tumors. *Pediatr Blood Cancer* 42:295-310, 2004
- Rao BN, Rodriguez-Galindo C: Local control in childhood extremity sarcomas: Salvaging limbs and sparing function. *Med Pediatr Oncol* 41:584-587, 2003

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The authors indicated no potential conflicts of interest.

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